

THE WELLCOME TRUST/ CANCER RESEARCH UK INSTITUTE

2003 PROSPECTUS/ANNUAL REPORT 2002

THE WELLCOME TRUST • CANCER RESEARCH UK •
Institute of Cancer and Developmental Biology







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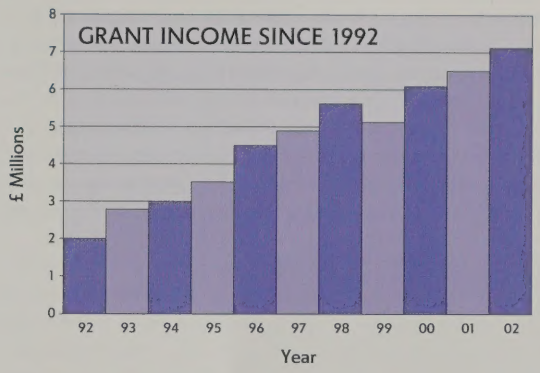
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CHAIRMAN'S INTRODUCTION

This will be our last year in the original Wellcome Trust/Cancer Research UK building, which we have occupied since 1990. Construction of our new building, funded by the Wellcome Trust and the Government's Office of Science and Technology, is well under way and will provide us with much improved laboratory space together with space for new core equipment. As the accompanying graphs show, the Institute has increased in size enormously over the past ten years, both in numbers and in grant income, and the move to new accommodation will relieve overcrowding and allow us to buy some much-needed equipment for which we have the money but not the space. The move should take place early in 2004.

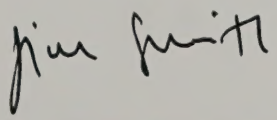


Our sixteen group leaders receive funding from one or other of our major sponsors: the Wellcome Trust and Cancer Research UK. We are pleased that Daniel St Johnston's Wellcome Trust Principal Research Fellowship was renewed this year, as was Azim Surani's Programme Grant. Andrea Brand also received a Programme Grant from the Wellcome Trust.



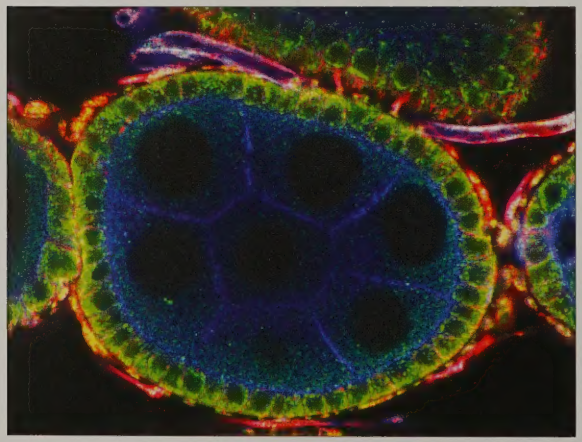
We were delighted that Anne McLaren was awarded the Japan Prize for 2002. This prestigious award recognises more recent achievements than does the Nobel Prize, and Anne and her co-awardee Andrzej Tarkowski received the prize in recognition of their efforts 'to unlock the mysteries of mammalian embryonic development'. Professor Tarkowski has another link with the Wellcome Trust/Cancer Research UK Institute in that he was the PhD supervisor of Magdalena Zernicka-Goetz, who was appointed as a Group Leader last year. Recipients of other honours and awards are listed on page 59.

This year saw the first Group Leaders' retreat. This was held in Ashridge, Hertfordshire, and allowed Group Leaders to discuss their work in more depth than is possible at the Institute Retreat. We hope to repeat the event next year.

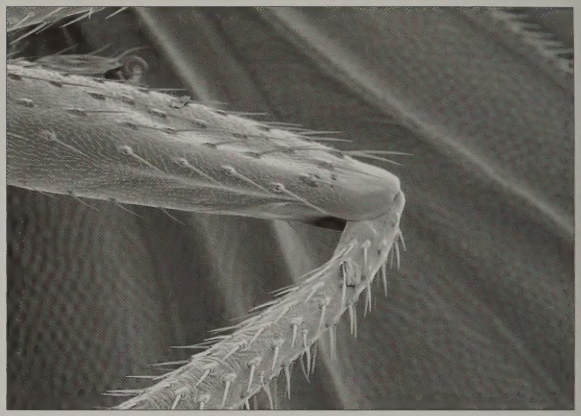


HISTORICAL BACKGROUND

The Institute is situated in the middle of the area containing the science departments of the University of Cambridge and within a short distance of the centre of the historic city. Founded in 1989 to promote research in the areas of developmental biology and cancer biology, the Institute is an assemblage of independent research groups located in one building designed to promote as much interaction as possible. Developmental and cancer biology are complementary since developmental biology is concerned with how cells acquire and maintain their normal function, whereas cancer is a result of a cell breaking loose from its correct controls and becoming abnormal. Both areas require a detailed knowledge of intercellular processes, which need to be analysed at the cellular and molecular levels. These research areas are complementary at the scientific and technical levels. To understand what goes wrong when a cell becomes cancerous requires a knowledge of the processes that ensure correct function in normal development. At the technical level, the analysis of cellular and molecular processes requires familiarity with techniques that no single person can master, such as gene cloning, antibody preparation, cell culture, microarray technology, imaging and embryonic manipulation. There is, therefore, a major benefit in having scientists with different but complementary knowledge and technical skills working in close proximity to one another.



An oocyte labelled with three different antibodies (Katja Röeper, 2002).



Drosophila leg and wing [x200] (Cathy Torgler, 2002).

The Institute is an integrated part of Cambridge University, and all Group Leaders are affiliated to a University Department and contribute to teaching and graduate student supervision.

CENTRAL SUPPORT SERVICES

Our core staff provide administrative, technical and computing support to the scientists, in order to ensure the smooth running of the Institute. As usual, these vital tasks have been performed efficiently and well in 2002 and we are grateful to every member of the team for their hard work and good humour.

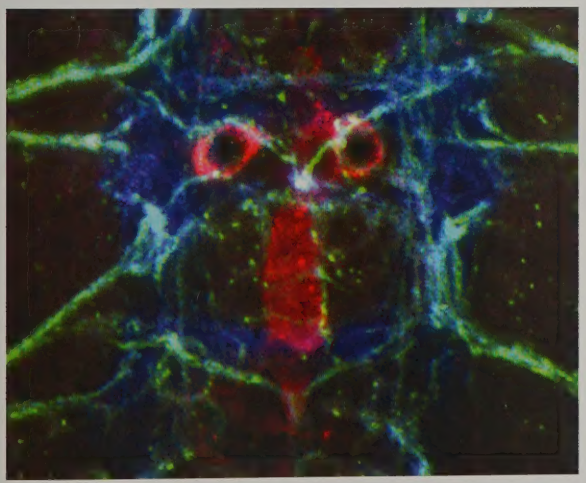
We said farewell this year to Janet Ferguson, who retired from her post as Chief Technician, a position she has held since the Institute was founded. Jane Cooper, our Chief Accountant for seven years, has left to work in another department in the University. We wish

them both well, and thank them for their long years of service to the Institute.

FUNDING

Our Institute receives core support from both the Wellcome Trust and Cancer Research UK. These charities also support the Institute in the form of Fellowships, individual programme and project grants and equipment grants.

Other sources of funding, both direct and indirect, include the European Community, BBSRC, MRC, the Royal Society, the Lister Institute of Preventive Medicine, the Elmore Trust, the Isaac Newton Trust, the Leverhulme Trust, the Association for International Cancer Research, the Human Frontier Science Program and the European Molecular Biology Organization. We are very grateful to all these organisations for their continuing support.



In *Drosophila* embryos, as in vertebrate embryos, a small subset of cells at the midline (red) of the developing CNS directs axonal pathfinding of the majority of motorneurons (green) and interneurons (blue) (Torsten Bossing, 2002).

INSTITUTE FACILITIES

Generous support from the Wellcome Trust and Cancer Research UK has ensured that the Institute has excellent facilities for its research. Both charities, for example, have recently provided us with state-of-the-art microarray facilities and we have also been fortunate to employ Mike Gilchrist as our Institute bioinformatician. Mike has been extraordinarily helpful to many members of the Institute already, allowing us to take advantage of our microarray data and of the expanding sequence databases.



NEW BUILDING

We expect to move into our new building in early 2004. The building will provide enhanced laboratory and communal facilities and more core equipment space. In particular, we will be able to accommodate our improved imaging, bioinformatics, proteomic and microarray facilities. Members of the Institute have already had an opportunity to look around the shell of the building and to imagine how their labs will look when the building is finished. A topping-out ceremony, held when the building reached its highest level, took place on 1st November 2002. The Vice Chancellor of the University, Sir Alec Broers, and Director of Sir Robert McAlpine, Ian McAlpine, attended. Finally, we should again like to thank our neighbours in the Biochemistry Department, for whom the work has caused some inevitable disruption, for their forbearance.



Institute staff on retreat at Lady Margaret Hall, Oxford (John Overton, 2002).

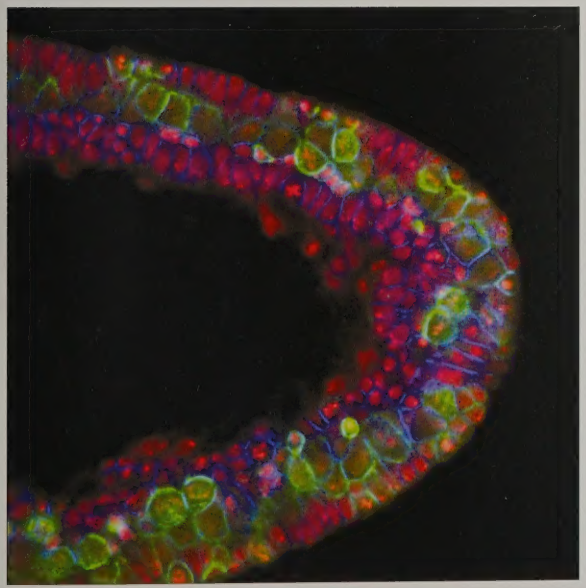
INSTITUTE RETREAT

This year our Institute Retreat was held at Lady Margaret Hall, Oxford on 23rd and 24th September. There was a strong attendance, and the whole occasion was scientifically and socially a great success. We thank Magdalena Zernicka-Goetz, Jon Pines, Julie Ahringer and our administrative team for their hard work in organising the event.

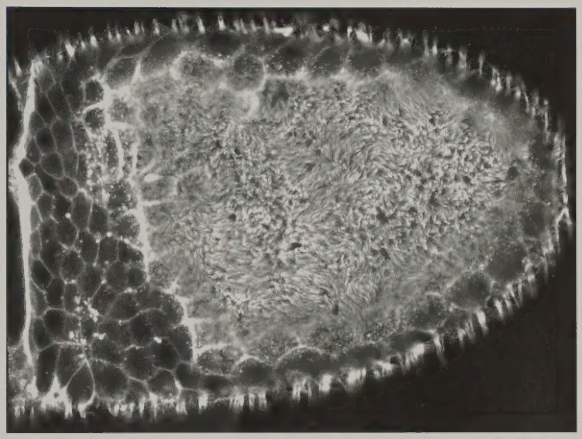
EXTERNAL ACTIVITIES

Members of the Institute have been active in organising local, national and international meetings. In Cambridge, Katja Röper and Patrick Western coordinate the weekly inter-departmental seminars in developmental biology, and Jordan Raff organises a *Cells Behaving Badly* Open Day every other year as part of the University's National Science Week. These have been extremely successful, attracting more than 200 visitors. In 2002, Cambridge also hosted the 9th International *Xenopus* Conference and the 3rd

International *Xenopus* Genomics and Genetics Meeting. The former, held in Homerton College, was organised by John Gurdon with help from Enrique Amaya, Nancy Papalopulu, Jim Smith and Caroline Webb. Generous sponsorship from a number of organisations (including the Wellcome Trust), an attendance of nearly 300 scientists from 15 countries and good weather all contributed to a highly successful event. The Genomics and Genetics Meeting was organised by Enrique Amaya and Rob Grainger (University of Virginia), with help from Juliet Barrows. The event was attended by 125 scientists from 13 countries, and one of the highlights was the announcement that the Joint Genome Institute (California) will sequence the genome of *Xenopus tropicalis*.



Dividing neuroblasts in a *Drosophila* embryo stained with Miranda (green), a membrane marker (blue) and DNA (red) (Claudia Barros, 2002).



Actin cytoskeleton in a *Drosophila melanogaster* egg chamber stained with rhodamin-phalloidin. (Isabel L Torres, 2002)

Elsewhere in the UK, Jim Smith and Ginny Papaioannou, (Columbia University, New York) organised a British Society for Developmental Biology meeting on *T box* genes in Development and Disease. Held in Nottingham, this was the first international meeting to discuss this important gene family. Meanwhile, Steve Jackson co-organised a meeting on Signalling the Future, a joint venture between the Biochemical Society and the University of Liverpool to celebrate the centenary of biochemistry in Liverpool and the UK. With 700 delegates and some excellent talks, this was a highly successful meeting. Steve also helped Tony Kouzarides organise the International Genes and Cancer meeting in Warwick, held just before Christmas 2002. The meeting focussed on molecular aspects of cancer cell function and about 300 people attended.

JULIE AHRINGER



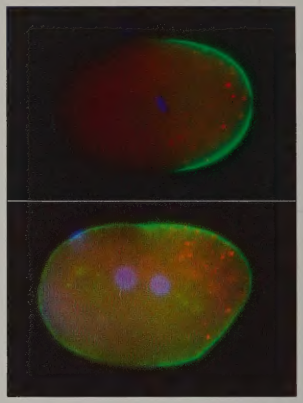
Co-workers:

Rob Andrews
Yan Dong
Nathalie Le Bot
Costanza Panbianco
Gino Poulin
Miao-Chih Tsai
Christine Turner
David Welchman
Peder Zipperlen

We have been studying how patterns of cell divisions and cell fates are controlled, using *C. elegans* as a model system. We have focussed on two major questions. First, how is cell polarity initially established and how is this information then transduced? Second, what is the role of repressive chromatin regulation during cell fate decisions? For both of these questions, we are taking advantage of a genome-wide RNA interference (RNAi) library we have constructed.

Cell polarity is an essential feature of many animal cells. For example, it is critical for epithelial formation and function and for correct partitioning of fate-determining molecules. We are using the one-celled *C. elegans* embryo as a powerful model system for studying cell polarity. We have shown that heterotrimeric G proteins transmit polarity information to the spindle and have identified many new polarity loci using genome-wide RNAi screening. We study these with a range of techniques, including videomicroscopy of live embryos.

Transcription repression mediated through histone deacetylase (HDAC) complexes is widespread, and mechanisms by which HDAC complexes act are emerging from *in vitro* and cell culture studies. However, little is known about the developmental roles of histone deacetylation. One of the major histone deacetylation complexes in animal cells is called NuRD (nucleosomal remodelling and histone deacetylase). In *C. elegans*, the NuRD complex is required to carry out a range of different cell fate decisions. We are studying how NuRD functions in development and are conducting genome-wide RNAi screens to identify new genes that cooperate with it.



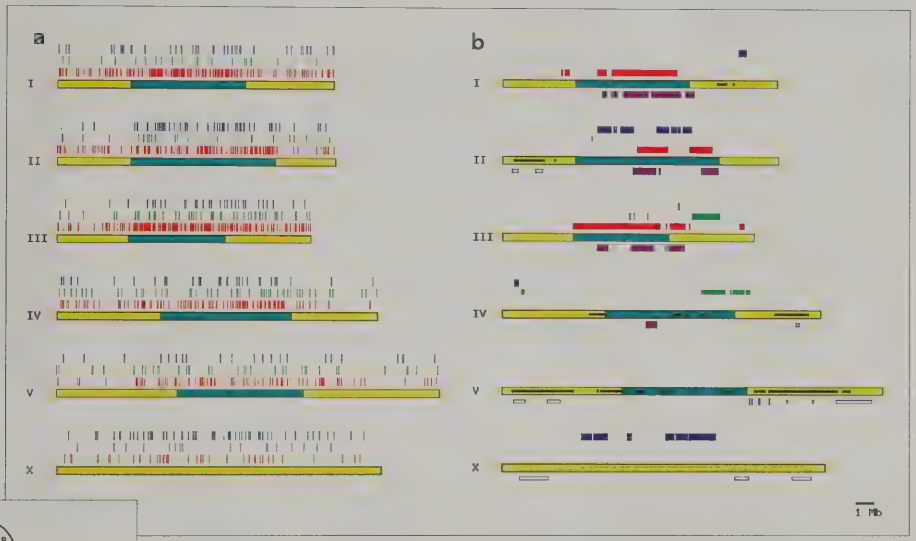
Posterior localisation of PAR-2:GFP (green) in a wild-type *C. elegans* embryo (above) is abolished in a new polarity mutant identified by RNAi screening (below). P granules (red) are localised to the posterior; DNA, blue.

Kamath RS, Fraser AG, Dong Y, Poulin G, Durbin R, Gotta M, Kanapin A, Le Bot N, Moreno S, Sohrmann M, Welchman D, Zipperlen P and Ahringer J (2003) Systematic functional analysis of the *C. elegans* genome using RNAi. **Nature** *421*, 231–237.

Ahringer J (2003) Control of cell polarity and mitotic spindle positioning in animal cells. **Curr. Opin. Cell Biol.** *15*, 73–81.

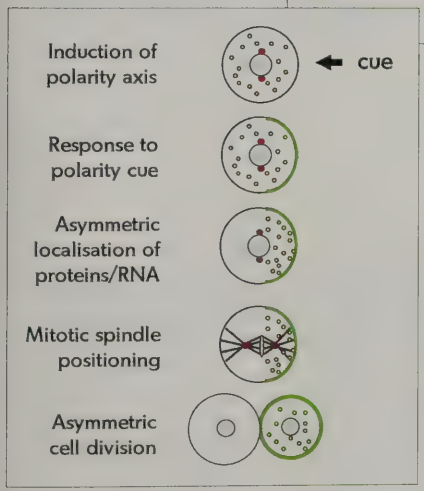
Solari F and Ahringer J (2000) NuRD complex genes antagonise Ras-induced vulval development in *C. elegans*. **Curr. Biol.** *10*, 223–226.

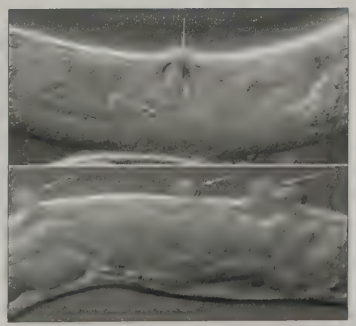
For further publications, see numbers 6, 22, 29, 34, 37, 61 and 89 on pages 53, 54, 56 and 57.



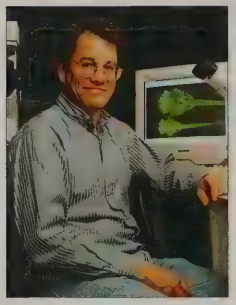
a) Each red, green, and blue tick represents the location of a gene with an RNAi phenotype on one of the six *C. elegans* chromosomes (yellow), identified in an RNAi screen of 16,757 genes; red: lethal phenotype; green: growth defect; blue: post-embryonic defect. b) Genes with similar functions are clustered in certain regions of the genome; colours are as for (a). Purple bars show correspondence of clustering of genes with a particular shared transcription profile with that of lethal genes.

Cell polarisation and asymmetric cell division processes are being studied in the one-celled *C. elegans* embryo.





The NuRD chromatin remodelling complex is involved in many cell fate decisions. Lack of NuRD function results in ectopic vulval tissue in the adult worm (arrows, bottom) due to inappropriate activation of the Ras pathway. Wild type (top).



Co-Workers:

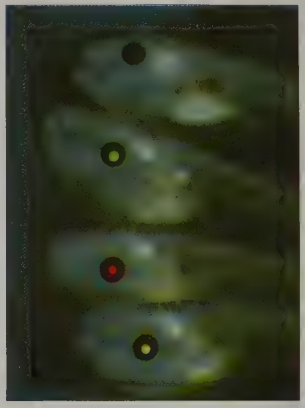
Juliet Barrows
Jun-An Chen
Ricardo Costa
Rosalind Friday
Kim Goldstone
Miranda Gomperts
Kathy Hartley
Shoko Ishibashi
Lars Petersen
Jeremy Sivak

One of the main interests of our group is understanding the molecular events responsible for mesoderm formation and patterning. In particular we are investigating the role of fibroblast growth factor (FGF) signalling during mesoderm formation in the frog, *Xenopus laevis*. We have shown that inhibiting FGF signalling during gastrulation disrupts mesoderm formation and morphogenesis. In order to better understand this process, we have begun to isolate downstream targets of FGF signalling. One target we have identified is the gene *Xsprouty2*. This gene has the interesting property that it is both a target of FGF signalling and a modulator of FGF signalling. We have begun to use bioinformatics in combination with functional screens to identify additional genes involved in mesoderm formation.

We are also studying how mesoderm pattern is established in the amphibian embryo by investigating the transcriptional regulation of two early mesodermal genes in transgenic embryos. One of these genes, *Xnot*, is expressed in dorsal mesoderm fated to become notochord and the other gene, *XMyf-5*, is a myogenic gene expressed in dorso-lateral mesoderm fated to become muscle.

In addition we are interested in investigating the role of growth factor signalling in patterning of the nervous system. For these studies we are using the binary Gal4-UAS mis–expression system. We have also begun to study the role of *Xenopus Dachshund* in the development of the nervous system.

Finally, we are performing an insertional mutagenesis screen using a gene trap approach in *Xenopus tropicalis*, a diploid frog related to *Xenopus laevis*, with a view to identifying novel genes involved in development.



A cross between two transgenic *Xenopus tropicalis* lines, one expressing green fluorescent protein in the lens (2nd from top) and the other expressing red fluorescent protein in the lens (3rd from top) gives rise to progeny with yellow lenses (bottom). Embryo at top is not transgenic.

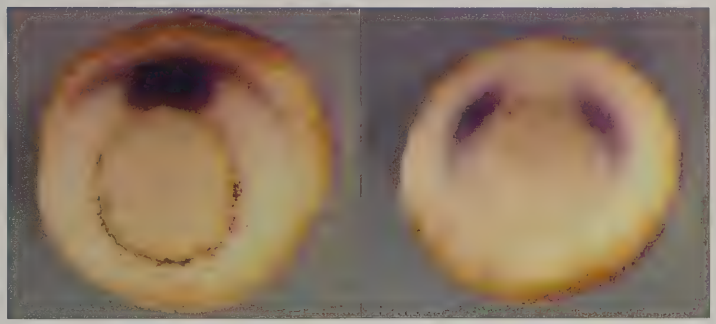
Nutt SL, Dingwell KS, Holt CE and Amaya E (2001) *Xenopus Sprouty2* inhibits FGF mediated gastrulation movements but does not affect mesoderm induction and patterning. **Genes Dev.** *15*, 1152–1166.

Hartley KO, Nutt SL and Amaya E (2002) Targeted gene expression in transgenic *Xenopus* using the binary Gal4-UAS system. **Proc. Natl Acad. Sci. USA** *99*, 377–382.

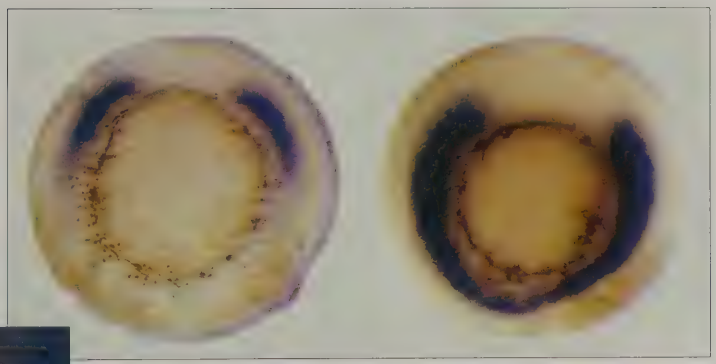
Polli MP and Amaya E (2002) A study of mesoderm patterning through the analysis of the regulation of *XMyf-5* expression. **Development** *129*, 2917–2927.

For further publications, see numbers 56 and 94 on pages 55 and 57.

At the gastrula stage *Xnot* is expressed in dorsal mesoderm fated to become notochord (left) and *Xmyf5* is expressed in dorso-lateral mesoderm fated to become muscle (right).



Injection of antisense morpholino oligonucleotides against *Xenopus tropicalis Xvent1* and *Xvent2* results in expansion of *Xmyf5* expression into the ventral marginal zone at the gastrula stage (right); control injected embryo (left).





Xenopus Dachshund 1 (XDach1) is expressed in the eye and hindbrain at the tailbud stage.

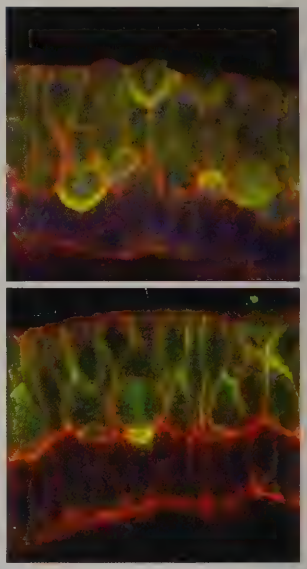
ANDREA BRAND



Co-workers:

Claudia Barros
Torsten Bossing
Adrian Carr
Semil Choksi
Melanie Cranston
Catherine Davidson
Catherine French
Michael Hewett
Vaishnavi Krishnan
Michael Murray
Peter van Roessel
John Solly
Christine Turner

We are interested in how cellular diversity is generated in the nervous system and in the signalling pathways that direct axon pathfinding and synaptic development. In the *Drosophila* CNS, neurons and glial cells arise from neural stem cells, or neuroblasts. Neuroblasts renew themselves at each division and give rise to smaller daughter cells called GMCs. Discovering how stem cells are maintained in a multipotent state and how their progeny differentiate into distinct cellular fates is of fundamental importance in understanding development. Our research focusses on how cellular diversity is generated by asymmetric stem cell division. A simple way to generate two different cell types is by the asymmetric partitioning of cell fate determinants. For example, the determinant Prospero is segregated from the neuroblast to its daughter at each division. We have shown that myosins, motor proteins that interact with the actin cytoskeleton, play an integral role in the asymmetric segregation of Prospero. Once in daughter cells, Prospero restricts their mitotic potential. We use time lapse confocal microscopy to follow asymmetric cell division in living embryos, and have fused different spectral variants of GFP to Prospero, myosin, actin and microtubules for double labelling *in vivo*. We are also characterising the role in development of the *Drosophila* Ephrin and Fer homologues, using classical and reverse genetic approaches such as ectopic expression and targeted RNAi to eliminate expression in specific cells. Using similar approaches we have demonstrated a novel function for the anaphase-promoting complex in post-mitotic cells: the regulation of synaptic growth and activity.



Cell fate determinants (green/yellow) are asymmetrically segregated from neuroblasts to their daughters in the early embryonic CNS (DNA labelled in blue, actin in red).

Kaltschmidt JA, Davidson CM, Brown NH and Brand AH (2000) Rotation and asymmetry of the mitotic spindle direct asymmetric cell division in the developing central nervous system. **Nat. Cell Biol.** *2*, 7–12.

Bellaiche Y, Gho M, Kaltschmidt JA, Brand AH and Schweisguth F (2001) Frizzled regulates the localization of cell-fate determinants and mitotic spindle rotation during asymmetric cell division. **Nat. Cell Biol.** 3, 50–57.

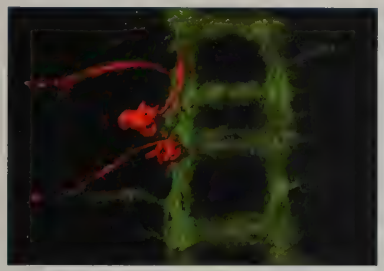
Bossing T and Brand AH (2002) Dephrin, a transmembrane ephrin with a unique structure, prevents interneuronal axons from exiting the *Drosophila* embryonic CNS. **Development** *129*, 4205–4218.

van Roessel P, Hayward NM, Barros CS and Brand AH (2002) Two-color GFP imaging demonstrates cell-autonomy of GAL4-driven RNA interference in *Drosophila*. **genesis** *134*, 170–173.

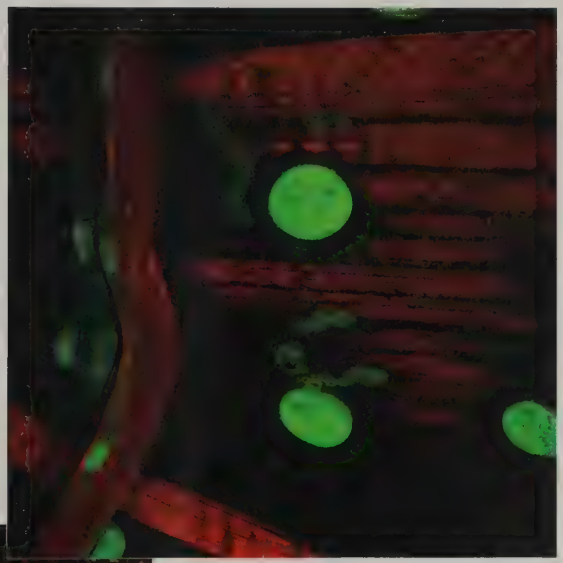
For further publications, see numbers 15, 18, 52, 54 and 80 on pages 53, 55 and 57.



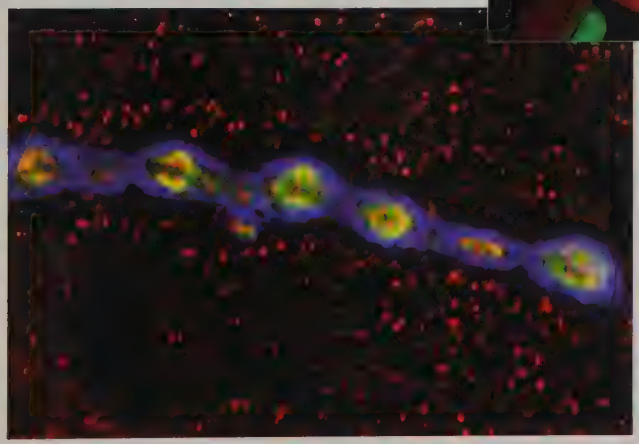
Live imaging of the RP2 motor neuron as it extends its axon out of the CNS towards its target muscle



Single cell labeling allows the analysis of the development and differentiation of neural cells in larval ganglions. 3D reconstruction of a neural clone (red), axons in green



A GFP fusion protein highlights synaptic junctions on larval muscles (GFP = green, actin = red)



A component of a ubiquitin ligase complex (red) co-localises with synaptic vesicles (green) at the neuromuscular synapse. Post-synaptic membrane in blue.



Co-workers:

Danelle Devenport
Jasmin Kirchner
Maithreyi Narasimha
John Overton
Katja Röper
Xiao Tan
Guy Tanentzapf
Cathy Torgler
Vikki Williams
Christos Zervas

Cellular adhesion and communication are vital during the development of multicellular organisms. These processes use proteins on the surface of cells, which stick cells together or transmit signals from outside the cell to the interior, so that the cell can respond to its environment. Members of one family of cell surface receptors, called integrins, can perform both of these activities, and therefore provide a molecular link between cell adhesion and signalling. Our research is focussed on determining how proteins inside and outside the cell assist the integrins in their developmental roles: mediating cell migration, adhesion between cell layers, and cell differentiation.

To discover what other proteins are required to work with the integrins, we have used the genetics of the fruit fly *Drosophila*. Loss of integrin function in the wing causes a characteristic blister phenotype, which we have used in our genetic screen. The molecular characterisation of the genes we identified is providing a description of the proteins that link integrins to the cytoskeleton. These proteins include the cytoskeletal linker proteins kakapo and talin, and the signalling adaptor proteins integrin-linked kinase and tensin. By manipulating the structure of these proteins and assaying their function in the living animal, we are elucidating how they contribute to integrin-mediated adhesion during development. In the past year, we have made particular progress in placing these integrin-associated proteins into a hierarchy. For example, talin has proven to be a core component, judging by the almost identical defects caused by the absence of integrins and talin.



Mutations in one of the new genes cause the wing blister phenotype characteristic of the loss of integrin-mediated adhesion between the two surfaces of the wing.

Bökel C and Brown NH (2002) Integrins in development: moving on, responding to, and sticking to the extracellular matrix. **Dev. Cell** *3*, 311–321.

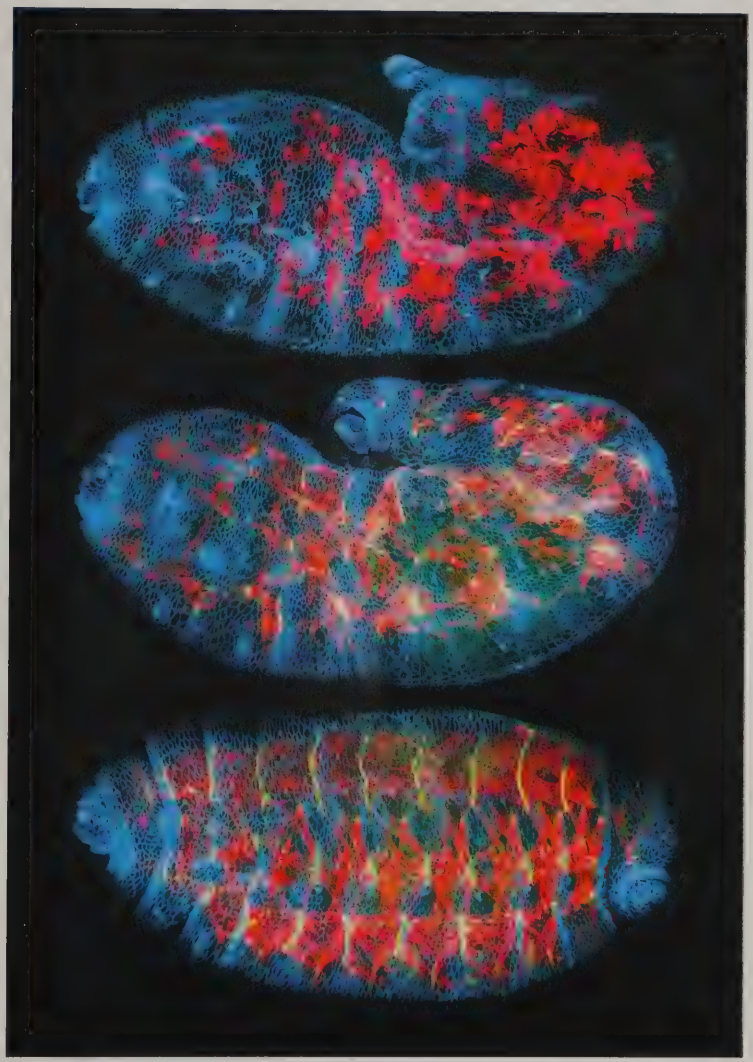
Zervas CG and Brown NH (2002) Integrin adhesion: when is a kinase a kinase? **Curr. Biol.** *12*, R350–R351.

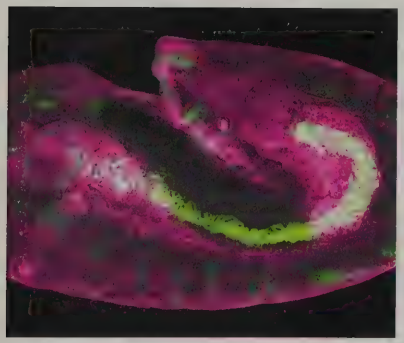
Röper K, Gregory SL and Brown NH (2002) The 'Spectraplakins': cytoskeletal giants with characteristics of both spectrin and plakin families. **J. Cell Sci.** *115*, 4215–4225.

Brown NH, Gregory SL, Rickoll WL, Fessler LI, Prout M, White RAH and Fristrom JW (2002) Talin is essential for integrin function in *Drosophila*. **Dev. Cell** *3*, 569–579.

For further publications, see number 58 and 106 on pages 56 and 58.

This figure shows the similarity in the defects caused by the absence of integrins (top) and talin (middle) compared to normal development (bottom). The embryo fails to "straighten up" as revealed by staining the epidermal cells in blue, and the muscles (red) detach when they start contracting. Integrin staining at the muscle attachment sites is shown in green/yellow.





Integrin-dependent migration of the primordial midgut cells (two large cell aggregates in purple) along a road made of visceral muscle cells (green)

JOHN GURDON



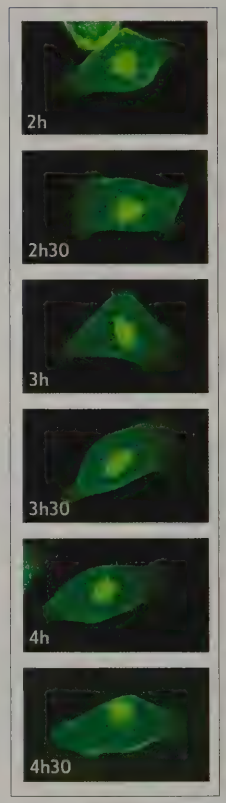
Co-workers:

James Byrne
Nigel Garrett
Oliver Grimm
Ray Kit Ng
Timothy Robinson
Stina Simonsson
Caroline Webb

Our group is interested in nuclear reprogramming and cell fate determination by signal factors in amphibian development. The transplantation of a nucleus from specialised tissue such as the intestine to an enucleated egg results in a rapid activation of early embryo genes. Our aim is to understand the molecular mechanism and to identify molecules required for nuclear reprogramming, in the expectation that these will throw light on normal mechanisms of gene regulation, and that they may help progress towards the direct nuclear reprogramming of somatic cells.

Early embryonic cells, whether obtained by fertilisation or by nuclear transfer, can be made to embark on diverse cell differentiation pathways by exposure to the appropriate concentration of signal factors such as activin or BMP4. Such factors are called morphogens, and operate widely in early development. We have determined the number of occupied receptors, the rapidity of intracellular Smad2 phosphorylation, and the real-time migration of GFP-Smad 2 to the nucleus. We aim to understand the principles by which a concentration-dependent signalling process is regulated so as to provide the right strength of signal at the right time. To progress from early embryo gene expression to a differentiated cell type, a community effect signalling within a group of like cells is often required.

The combination of nuclear transfer, morphogen signalling, and a community effect can generate cells of one kind, such as muscle, from cells of another kind, such as intestinal epithelium. Further work of this type could lead to a route for cell replacement.



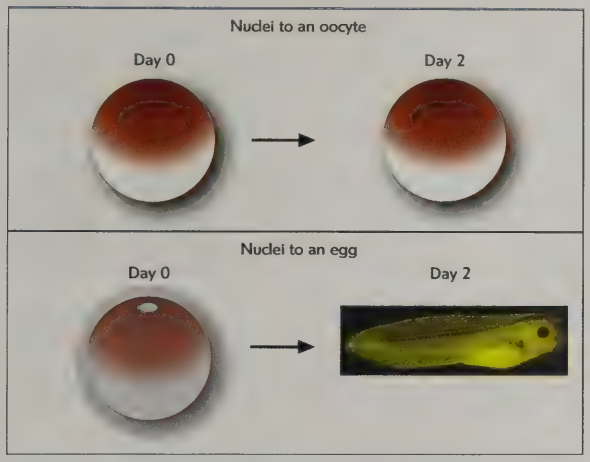
Hours after a 10min activin treatment: GFP Smad2 continues to enter the nucleus for several hours after removal of extracellular activin.

Gurdon JB and Bourillot P-Y (2001) Morphogen gradient interpretation. **Nature** *413*, 797–803.

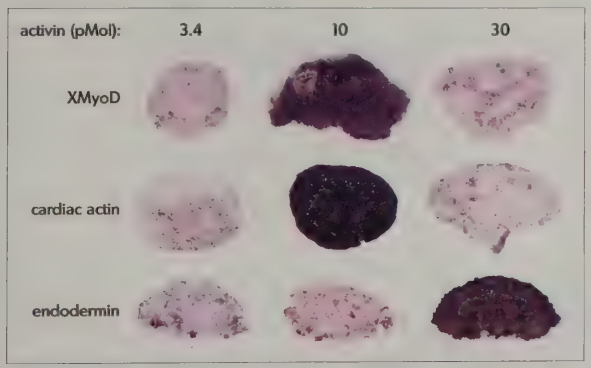
Bourillot P-Y, Garrett N and Gurdon JB (2002) A changing morphogen gradient is interpreted by continuous transduction flow. **Development** *129*, 2167–2180.

Freeman M and Gurdon JB (2002) Regulatory principles of developmental signalling. **Annu. Rev. Dev. Biol.** *18*, 515–539.

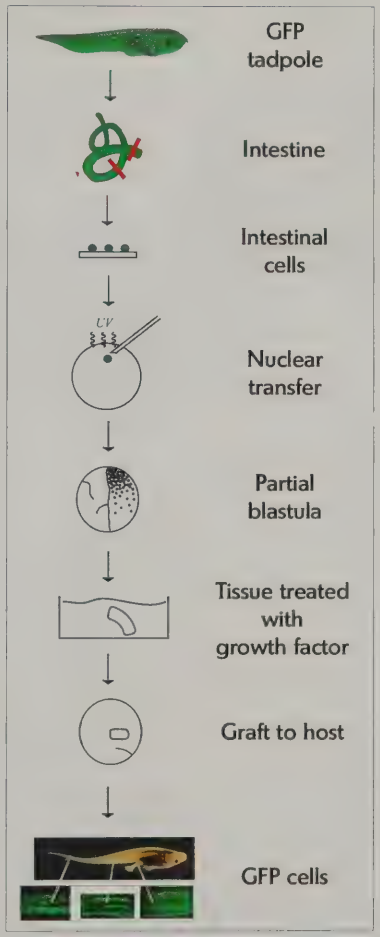
For further publications, see numbers 21, 43, 44, 56, 90, 94 and 96 on pages 53, 55 and 57.



What happens to cells that receive transplanted nuclei? An oocyte, with a transplanted nucleus, remains in culture for several days with no morphological change. An egg, with a transplanted nucleus, develops into a tadpole.



Homogeneous differentiation of blastula cells after treatment with an appropriate concentration of activin, followed by community effect communication within a group of cells.



Transdifferentiation by nuclear transfer and morphogen action



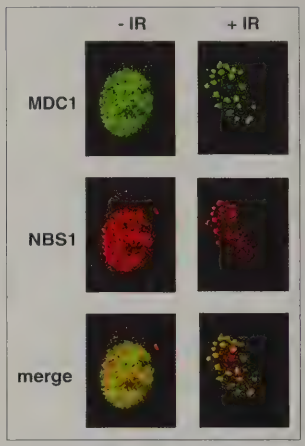
Co-workers:

Peter Ahnesorg
Jane Bradbury
Richard Chahwan
Julia Coates
Fabrizio d'Adda di Fagagna
Sabrina Giavara
Michal Goldberg
Serge Gravel
Muriel Grenon
Andrew Hammet
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Philip Reaper
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Joanne Slator
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Veronique Smits
Manuel Stucki
Soo-Hwang Teo

Agents that damage DNA continually bombard our cells. To maintain their genome integrity, our cells, like those of all other eukaryotes and also prokaryotes, have complex mechanisms for detecting DNA damage, signalling that damage has occurred, and repairing it effectively. We are studying these aspects of genome maintenance biochemically and genetically in mammalian and yeast cells and, most recently, in bacteria.

In yeast, we have gained important insights into the detection and signalling of DNA damage. Recently, we discovered Lcd1p, a *Saccharomyces cerevisiae* protein that functions close to the start of the signalling cascade that leads to a plethora of events, including cell-cycle arrest, in response to DNA damage. We have also identified a human protein, MDC1, that recruits the MRE11 complex to sites of DNA damage. This highly conserved, multifunctional protein complex comprising MRE11, RAD50 and NBS1 is involved in the detection and processing of DNA damage and in initiating an S-phase DNA-damage checkpoint.

Finally, we have gained some intriguing insights into the evolution of non-homologous end joining (NHEJ), a major repair pathway for DNA double-strand breaks. With our collaborator Aidan Doherty (Cambridge Institute for Medical Research, UK), we have identified several bacterial homologues of the Ku protein, a central molecule in eukaryotic NHEJ. We have obtained experimental data suggesting that these have similar properties to eukaryotic Ku, thus providing some of the first evidence for an NHEJ-like pathway in prokaryotic cells.



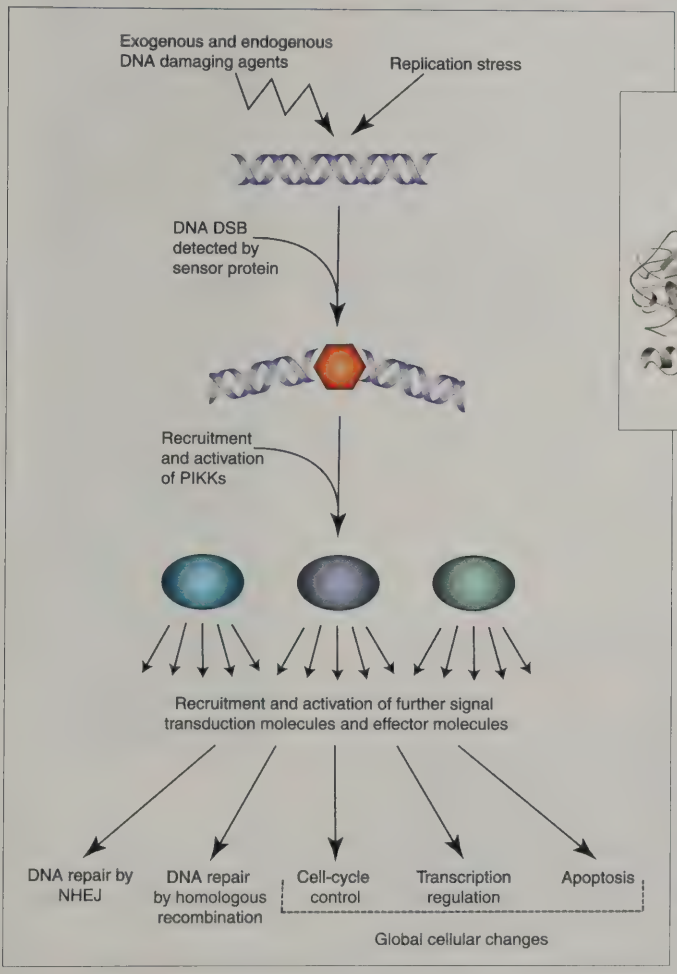
MDC1 and the MRE11/RAD50/NBS1 complex form nuclear foci in HeLa cells after exposure to ionising radiation. Here, cells are double stained with antibodies to MDC1 (green) and NBS1 (red) in the absence of irradiation or 6 hours after irradiation. The bottom right panel shows colocalisation of the foci in the nucleus after irradiation (yellow).

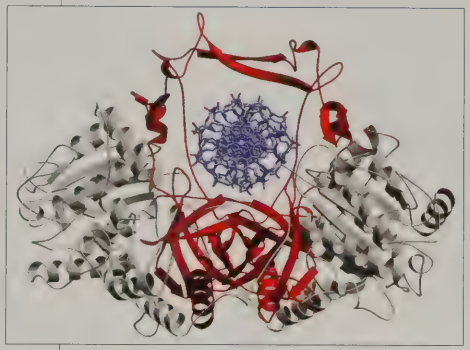
Rouse J and Jackson SP (2002) Interfaces between the detection, signaling and repair of DNA damage. **Science** *297*, 547–551.

Rouse J and Jackson SP (2002) Lcd1p recruits Mec1p to DNA lesions *in vitro* and *in vivo*. **Mol. Cell** *9*, 857–869.

Weller GR, Kysela B, Roy R, Tonkin L, Scanlan E, Della M, Krogh Devine S, Day JP, Wilkinson A, d'Adda di Fagagna F, Devine K, Bowater RP, Jeggo P, Jackson SP and Doherty AJ (2002) Identification of a DNA non-homologous end-joining complex in bacteria. **Science** *297*, 1686–1689.

For further publications, see numbers 2, 9, 23, 26, 33, 51, 53 and 62 on pages 53–56.





Prokaryotic Ku orthologues contain only the core DNA binding portion of eukaryotic Ku. The figure shows a dimer of eukaryotic Ku in which the region present in the prokaryotic orthologue, as deduced from sequence alignments, is picked out in red. The central blue/grey structure represents DNA.

Sensors, including Ku and Lcd1p, initially detect DNA double-strand breaks (DSBs). Amplification of the signals from sensors occurs first through recruitment and activation of a family of phosphatidylinositol kinase-like kinases (PIKKs). These phosphorylate downstream signal transduction molecules, proteins such as MDC1 in human cells and Rad9p in *S. cerevisiae*, that act as adaptors to facilitate signal transduction, and effector molecules that produce the appropriate cellular changes and the ultimate repair of the DSB.



Co-workers:

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Karen Halls
Luke Hughes-Davies
Paul Hurd
David Lando
Emma Langley
Steven Sanders
Helena Santos Rosa
Robert Schneider
Daniel Wolf

Many transcriptional regulators are de-regulated in cancer. Our group is interested in defining the mechanisms by which such transcription factors function during normal cell proliferation and in cancer.

Our attention is focussed on a set of enzymes that modify histones and regulate transcription via chromatin remodelling. We would like to understand the biological role of these enzymes and how their function is de-regulated in cancer. There are many covalent modifications that are deposited on the histones by chromatin-modifying enzymes. These include acetylation, methylation, phosphorylation and ubiquitination. We are interested in the mechanism by which these modifications regulate chromatin structure and ultimately control gene expression.

Most recently we have been focussing on the process of histone methylation. We have found that methylation of lysine 9 on histone H3 mediates transcriptional repression of genes regulated by the RB tumour suppressor, and functions by recruiting the HP1 protein to chromatin. In contrast, methylation of lysine 4 on histone H3 activates gene expression in a manner dependent on its methylation state. We are currently using, in addition to mammalian cells, model organisms such as yeast and *C. elegans* to identify new enzymes and characterise new modifications.

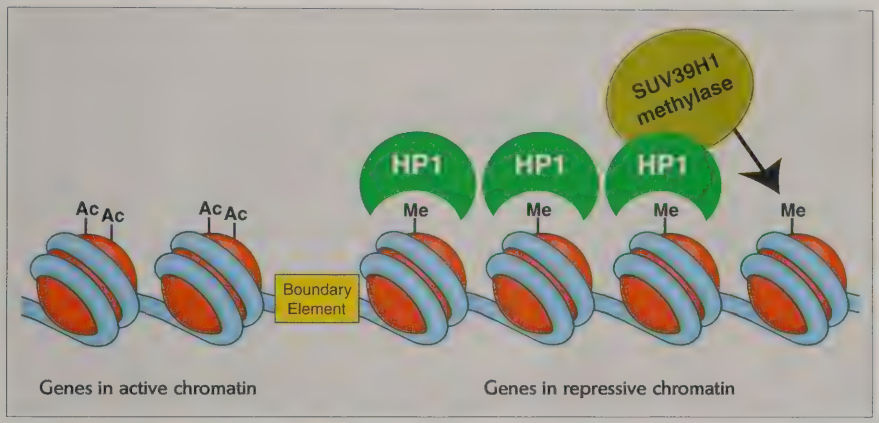


Santos-Rosa H, Schneider R, Bannister AJ, Sherriff J, Bernstein B, Tolga Enre NC, Schrieber SL, Mellor J and Kouzarides T (2002) Active genes are tri-methylated at K4 of histone H3. **Nature** *419*: 407–411.

Langley E, Pearson M, Faretta M, Bauer U-M, Frye RA, Minucci S, Pelicci PG and Kouzarides T (2002) Human SIR2 deacetylates p53 and antagonizes PML/p53-induced cellular senescence. **EMBO J.** *21*, 2383–2396.

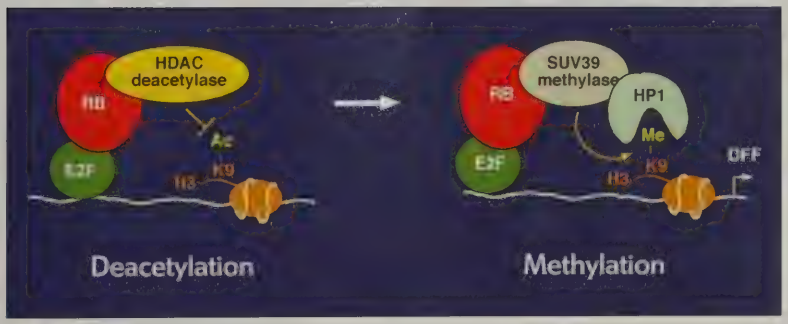
Daujat S, Bauer U-M, Shah V, Turner B, Berger S and Kouzarides T (2002) Cross-talk between arginine methylation and acetylation on histone H3. **Curr. Biol.** *12*, 2090–2097.

For further publications, see numbers 4, 7, 8, 12, 20, 25, 28, 30, 36, 57, 59, 67, 70, 74, 87, 88, 102 and 104 on pages 53–58.



Silencing of genes in centromeric heterochromatin involves spreading of HP1 via its ability to bind methylated histones.

Facing page:
Expression of the SIRT1 deacetylase in mouse embryo fibroblasts inhibits acetylation of p53. (in collaboration with Mark Pearson, Saverio Minucci and Pier Guiseppe Pelicci, European Institute of Oncology, Milan)



Repression by the retinoblastoma protein (RB) involves histone deacetylation followed by histone methylation.



Co-workers:

Juliet Barrows
Grace Nisbet
Sabhi Rahman
Stephen Sansom
James Smith
Uruporn Thammongkol

We study how different neurons are generated in a stereotyped order from the available pool of dividing stem and progenitor cells during development of the mouse central nervous system. Neural cell fate determination is controlled by a combination of extrinsic and intrinsic factors, including temporal changes in the ability of progenitor cells to generate different cell types. We study neural cell fate determination primarily in the mouse neocortex. This is the part of the brain that integrates sensations, is responsible for cognition and perception, and is a region of the nervous system unique to mammals.

The neocortex is a sheet-like structure composed of six cellular layers that are generated in order during development. However, the neocortex is modular, having areas primarily dedicated to different functions, including motor control and the somatic senses. There are marked differences between different cortical areas in the size of each layer, in terms of cell numbers and their connections, and the initial formation of areas is controlled at the level of cell fate determination in neural progenitor cells. Examples of our current research include:

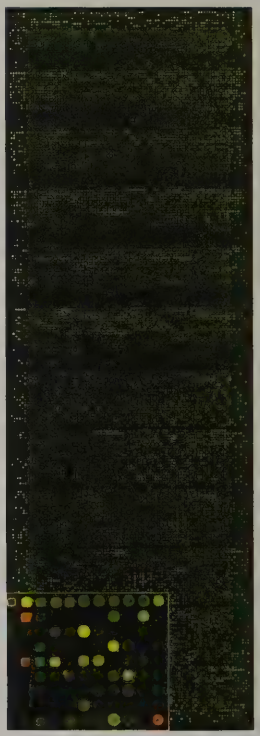
1) Studying the genetic basis for the formation of functional areas of the neocortex by expression profiling of neocortical stem and progenitor cells;

2) Microarray characterisation of the transcriptional responses of progenitor cells to extracellular factors implicated in generating the different functional areas;

3) Identifying the *in vivo* targets of transcription factors required for cortical development;

4) The identification of gene expression networks involved in laminar (cell layer) cell fate determination in the neocortex, using single cell expression profiling;

5) Functional studies of genes identified by these approaches using *in vitro* model systems of cortical development.



Mouse microarray of over 22000 oligonucleotides, representing a large proportion of the protein-coding genes expressed from the mouse genome. Inset is a detail of part of the array (James Smith)

Livesey R (2002) Have microarrays failed to deliver for developmental biology? **Genome Biol.** *3*, 2009.1–2009.5.

Blackshaw S and Livesey FJ (2002) Applying genomics technologies to neural development. **Curr. Opin. Neurobiol.** *12*, 110–114.

Livesey R and Cepko C (2001) Neurobiology: developing order. **Nature** *413*, 471–473.



Expression of an FGF receptor in the developing mouse forebrain. The receptor is localised to progenitor cells in subcortical structures, and shows a gradient of expression across the neocortex (Grace Nisbet)



Whole mount *in situ* hybridisation for a gene showing regional gene expression in the developing mouse neocortex

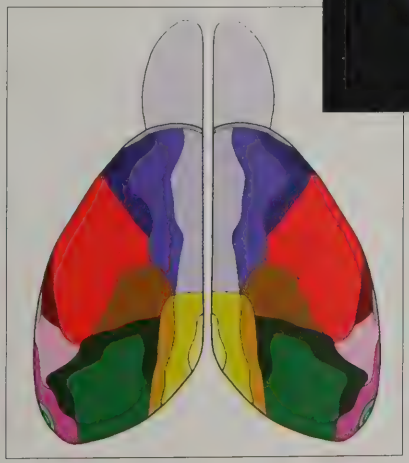
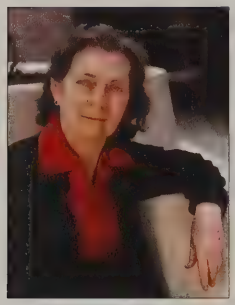


Diagram of a dorsal view of the adult mouse brain, showing the known anatomical and functional areas. Redrawn from Wree et al, Anat. Embryol., 1983 (Stephen Sansom)



Co-Workers:

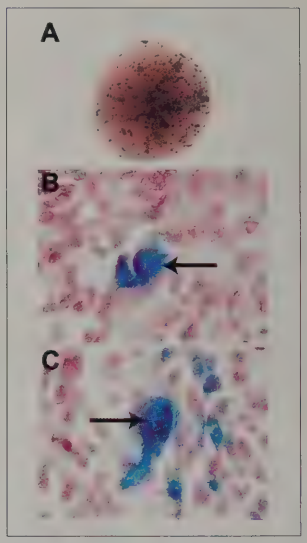
Ian Adams
Dilly Bradford
Gabriela Durcova-Hills

Our research focusses on mouse primordial germ cells (PGCs) and the pluripotent stem cells derived from them.

We have established that prenatal entry into meiosis, the prelude to oogenesis, occurs spontaneously in both XX and XY germ cells, but is blocked in the male genital ridge. In a search for the molecular basis of this masculinising influence, we identified a gene that codes for the signalling molecule prostaglandin D2. Normally expressed in the male genital ridge, prostaglandin D2 can induce partial masculinisation of both somatic and germ cells in female genital ridges *in vitro*. We are now investigating some of the other genes that have come out of our screening programme, including one with an expression pattern resembling that of *Oct4*.

The transition from a germ cell to a pluripotent embryonic germ cell (EGC) phenotype requires exposure to a cocktail of growth factors in the culture medium (for example bFGF, LIF, membrane-bound SCF). We have shown that 10 days of culture under these conditions is sufficient to achieve the shift to pluripotency in some of the primordial germ cells, as judged by their ability to colonise somatic lineages in chimeras. We are now examining the effect of shorter periods of exposure to individual factors, as well as the possibilities for directed differentiation of EGCs, in particular into cartilage and bone.

We are also investigating whether sex differences in the degree of hypomethylation of some imprinted genes in EGCs reflect genotypic or phenotypic sex, using EGC lines derived from sex-reversed and control embryos.



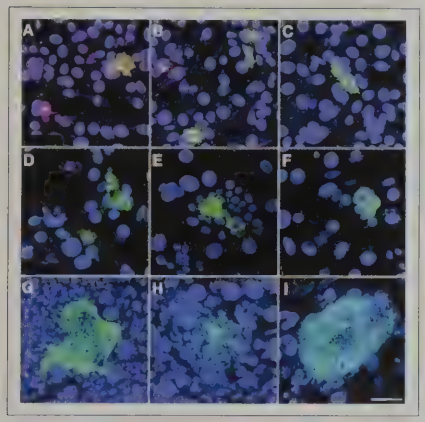
Male PGCs can be transfected without disrupting their development
11.5 dpc male PGCs were transfected with β-galactosidase. (A) Low magnification of an aggregate after 4 days culture, stained for β-galactosidase. (B) and (C) High magnification of sections through the stained aggregate, showing transfected prospermatogonia (arrows).

Nesterova NR, Mermoud JE, Hilton K, Pehrson J, Surani MA, McLaren A and Brockdorff N (2002) *Xist* expression and macroH2A1.2 localisation in mouse primordial and pluripotent embryonic germ cells. **Differentiation** *69*, 216–225.

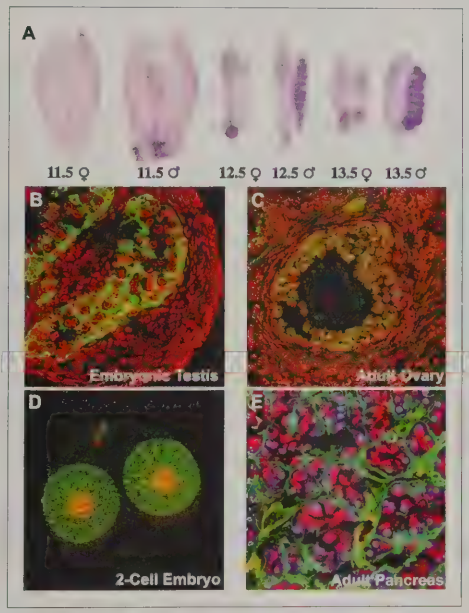
Adams IR and McLaren A (2002) Sexually dimorphic development of mouse primordial germ cells: switching from oogenesis to spermatogenesis. **Development** *129*, 1155–1164.

McLaren A (2002) Introduction, 9–14; Conclusion, 169–172. In: **Cloning** (co-ord. A McLaren). Council of Europe, Strasbourg.

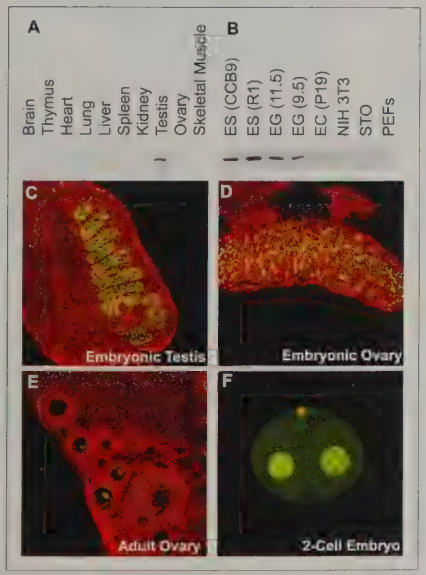
For further publications, see numbers 32 and 65 on pages 54 and 56.



11.5 dpc PGCs cultured on feeder cells with LIF and bFGF were stained for SSEA1 (green) and MVH (red). (A-C) After 1 day, some PGCs express both SSEA1 and MVH (A, B), some only SSEA1 (B,C), and a few express only MVH (A). (D-F) After 3 days, the PGCs had formed either PGC-like colonies with motile cells (D), or EGC-like colonies with non-motile cells (F). Some mixed colonies were also observed (E). (G-I) After 6 days, we identified large EGC-like colonies (I) mixed colonies (G) and colonies containing cells with fragmented SSEA1 expression (H).



Sexually dimorphic expression of Sup50.
(A) Expression of Sup50 mRNA in embryonic testis cords from 12.5 dpc, but not in the embryonic ovary. (B) Sup50 protein (green) is localised to the Sertoli cell cytoplasm which surrounds the germ cells in 13.5 dpc embryonic testis cords. (C, D) In adult ovaries, Sup50 (green) is expressed in the cytoplasm of follicle cells and oocytes, and in 2-cell stage embryos (E) Sup50 (red) is localised to the apical surface of adult pancreatic acinar cells



(A, B) Western blot of m7 protein in adult tissues (left) showing expression in the testis, and in cell lines (right) showing expression in pluripotent cell types but not in fibroblasts. (C-F) m7 protein (green) is present in the nuclei of male and female germ cells during gonad development, in the nuclei of growing oocytes in adult ovaries, and in the nuclei of pre-implantation embryos



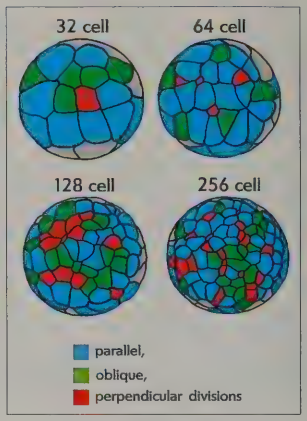
Co-Workers:

Eva Asscher
Juliet Barrows
Samantha Carruthers
Andrew Chalmers
Julia Mason
Tarik Regad
Bernhard Strauss
Jana Voigt

During embryonic development, neuroectodermal cells exit the cell cycle and differentiate in a stereotypical spatial and temporal pattern. The spatial and temporal control of neurogenesis is important for regulating cell type specification and the final number of differentiated cells. To understand how this control is achieved, we use the frogs *Xenopus laevis* and *Xenopus tropicalis* as model systems and a combination of molecular and classical embryology.

We are interested in the mechanisms that exert positive and negative control on neuronal differentiation. We are studying the regulation exerted by cell cycle inhibitors, such as $p27^{Xic1}$ and regional transcription factors, such as *XBF-1*. We have found that neuronal differentiation is additionally controlled by the intrinsically different capacities of progenitor cells to differentiate. Recently, we have discovered that this intrinsic difference is the result of asymmetric cell divisions that take place at the blastula stage. These divisions generate inner and outer cells and segregate membrane-localised aPKC to the apical membrane of the outer cells. Outer and inner cells become late and early differentiating progenitors, respectively, and the role of aPKC in this decision is currently being investigated. Microarray screening projects are also under way to identify novel determinants involved in making outer cells different from inner ones.

In parallel, gain- and loss-of-function screens have begun to uncover novel genes that affect neural development.



Oriented divisions start at the 32-cell stage and continue for several cell cycles. Blastomeres (coloured red) undergo perpendicular divisions and give rise to inner cells.

Chalmers A, Welchman D and Papalopulu N (2002) Intrinsic differences between the superficial and deep layers of the *Xenopus* ectoderm control primary neuronal differentiation. **Dev. Cell** *2*, 171–182.

Hartley KO, Hardcastle Z, Amaya E and Papalopulu N (2001) Transgenic *Xenopus* embryo reveal that anterior neural development requires continued suppression of BMP signalling after gastrulation. **Dev. Biol.** *238*, 168–184.

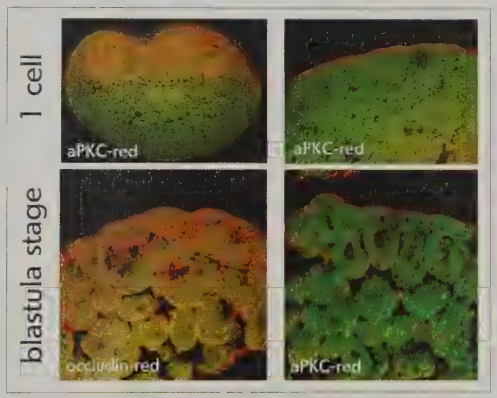
Khokha MK, Chung C, Bustamante EL, Gaw LWK, Trott KA, Yeh J, Lim N, Lin J, Taverner N, Amaya E, Papalopulu N, Smith JC, Zorn A, Harland RM and Grammer TC (2002) Techniques and probes for the study of *Xenopus tropicalis* development. **Dev. Dyn.** *225*, 499–510.

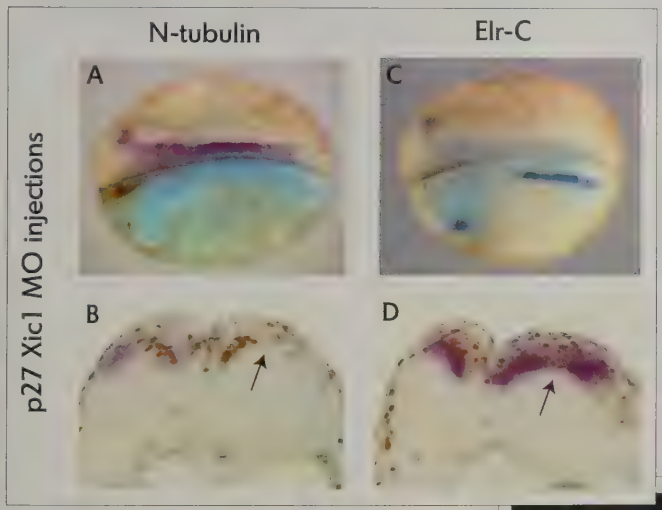
For further publications, see numbers 56 and 94 on pages 55 and 57.



A novel gene, expressed in the anterior neural plate (A; purple), was identified in a loss-of-function screen as a gene necessary for forebrain development. Morpholino-mediated knockdown causes a dramatic narrowing of the forebrain (C)

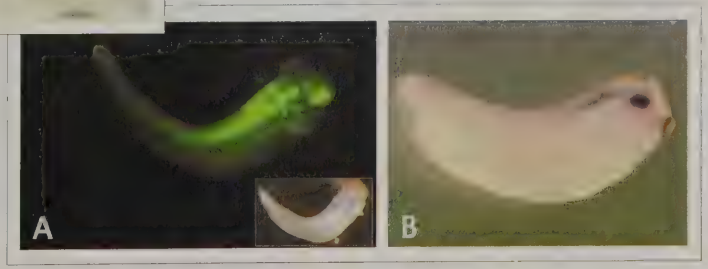
aPKC is localised to the membrane of the fertilised egg (1 cell stage). At the blastula stage, outer cells are polarised, with membrane localised aPKC only on the apical side, while inner cells are apolar





Knocking down of *p27*^{Xic1} by morpholino injections, impairs neuronal differentiation (A, arrow in B) and increases the number of proliferating progenitors (C, arrow in D). Injected side: light blue; BrdU incorporation: brown nuclei; *N-tubulin* and *ElrC* marker gene expression: purple.

A *p27*^{Xic1} genomic fragment drives GFP expression in the neural tube and eye, as shown by fluoresence (A) or by *in situ* hybridisation to GFP (B)



JONATHON PINES



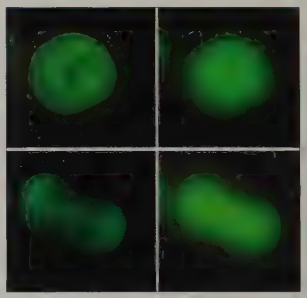
Co-workers:

Claire Acquaviva
Caroline Broad
Lorena Clay
Anja Hagting
Mark Jackman
Lars Koop
Catherine Lindon
Takahiro Matsusaka
Jo Richardson
Adam Walker

We are studying how cells divide and are focussing on two main aspects of cell division: how the cell first initiates mitosis, and how the cell co-ordinates mitosis by ubiquitin-mediated proteolysis. We are assaying these processes in real time by time-lapse fluorescence microscopy, using FRAP and photo-activation to gain a better understanding of the dynamics of protein behaviour, and deconvolution to improve the spatial resolution of our imaging.

We use GFP-fusion proteins to analyse the behaviour of cell cycle regulators in living cells. We use this assay to determine how their localisation is altered depending on the stage of the cell cycle, and to define the domains of the proteins that target them to specific subcellular structures. After defining these domains, we use them to isolate the proteins that are responsible for targeting and controlling the individual mitotic regulators.

To understand how proteolysis is used to regulate progress through mitosis, we assay the degradation of the GFP-fusion proteins in living cells, because their fluorescence is directly related to their protein level. We are studying the behaviour of key substrates at each stage of mitosis to define the events and the mechanisms that trigger the destruction of specific proteins at specific times. We are also investigating whether the ubiquitination machinery is spatially regulated in mitosis, in particular whether this is responsible for the exquisite control of protein degradation by the spindle assembly checkpoint.



HeLa cells expressing Cdc20-GFP in metaphase (top) and anaphase (bottom). The images on the left are derived by deconvolution from those on the right.

Jackman M, Lindon C, Nigg EA and Pines J (2002) Active cyclin B1-Cdk1 first appears on centrosomes in prophase. **Nat. Cell Biol.** *5*, 143–148.

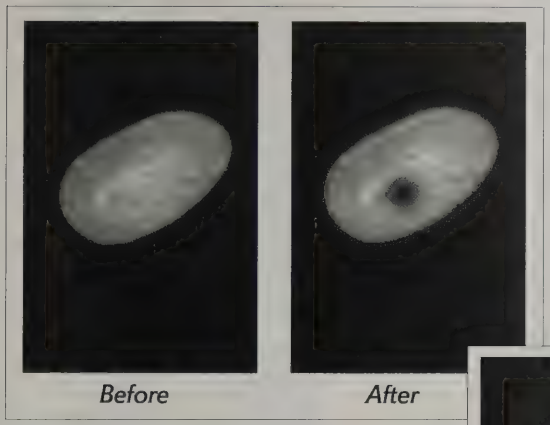
Hagting A, den Elzen N, Vodermaier HC, Waizenegger IC, Peters J-M and Pines J (2002) Human securin proteolysis is controlled by the spindle checkpoint and reveals when the APC/C switches from activation by Cdc20 to Cdh1. **J. Cell Biol.** *157*, 1125–1137.

Jackman M, Kubota Y, den Elzen N, Hagting A and Pines J (2002) Cyclin A- and cyclin E-CDK complexes shuttle between the nucleus and the cytoplasm. ***Mol. Biol. Cell*** *13*, 1030–1045.

For further publications, see numbers 24 and 69 on pages 54 and 56.

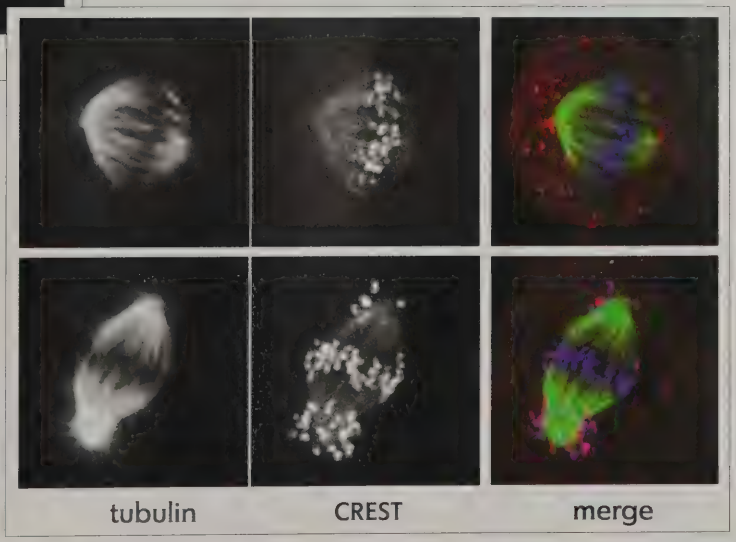
Photoactivation
HeLa cells expressing histone H2B linked to a photoactivatable form of GFP. A small area of the nucleus was irradiated with 457 nm laser light and the cell imaged using a GFP filter set. Only the photoactivated H2B-GFP is visible





FRAP
HeLa cells expressing histone H2B linked to GFP. A small area of the nucleus was irradiated with 488 nm laser light to bleach the GFP, and the cell imaged using a GFP filter set. A bleached area is clearly visible

How do cells regulate the plane of division? HeLa cells stained with CREST antiserum to stain the centromeres (blue), anti-Mad2 (red) and anti-tubulin (green)



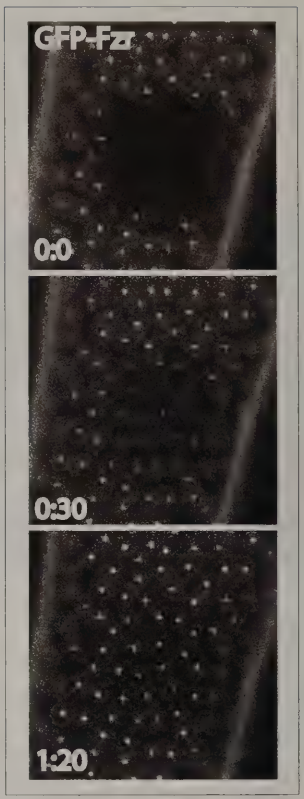


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Sue Croysdale
Annegret Finlay
Fanni Gergely
Junyong Huang
Michael Lee
Maruxa Martinez-Campos

The centrosome is the main microtubule-organising centre in animal cells. Despite its central role in organising many cellular events, very little is known about how centrosomes function. Using *Drosophila* as a model system, we have isolated proteins that bind to microtubules *in vitro* and associate with centrosomes *in vivo*. One of these proteins, D-TACC, interacts with microtubules in association with Minispindles (Msps), the *Drosophila* homologue of XMAP215, a well-characterised *Xenopus* microtubule-stabilising protein that is also concentrated at centrosomes. D-TACC is required to recruit Msps efficiently to centrosomes, and this appears to play a crucial role in regulating the stability of centrosomal microtubules in *Drosophila* embryos and in *Xenopus* embryo extracts. The human homologues of both D-TACC and Msps have been implicated in cancer, but their function in human cells is unclear. We have shown that hTACC3 appears to stabilise spindle microtubules by recruiting ch-TOG, the human homologue of Msps, to the spindle microtubules. In addition, however, ch-TOG appears to play an important role in organising mitotic spindle poles

Many cell cycle regulators are associated with centrosomes and we are analysing the role of the centrosome in regulating cell cycle events. We have shown that centrosomes are required to initiate the destruction of cyclin B in *Drosophila* embryos. The *Drosophila* anaphase promoting complex (APC), however, is not strongly concentrated at centrosomes, although two regulators of the APC (Fzy and Fzr) are both concentrated at centrosomes. We are currently testing whether this centrosomal localisation is important for regulating the exit from mitosis.



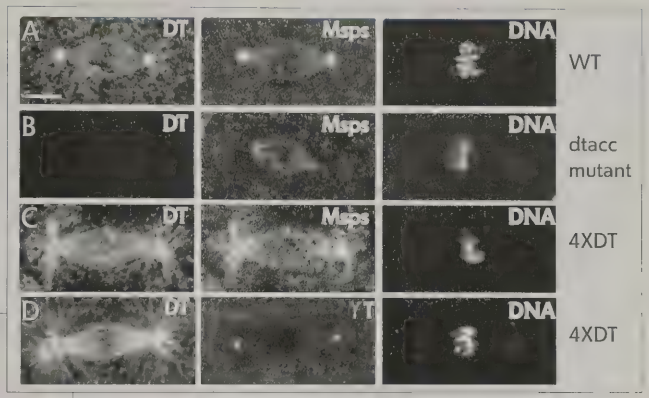
Gergely F, Draviam VM and Raff JW (2003) The centrosomal proteins TACC3 and ch-Tog are essential for mitotic spindle function in human cells. **Genes Dev.** *in press*.

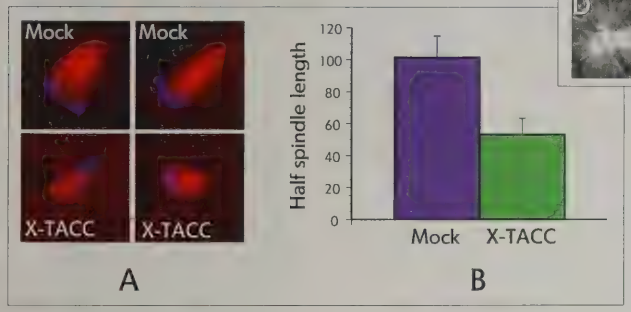
Huang J-Y and Raff JW (2002) The dynamic localisation of the *Drosophila* APC/C: evidence for the existence of multiple complexes that perform distinct functions and are differentially localised. **J. Cell Sci.** *115*, 2847–2856.

Raff JW, Jeffers K, and Huang J-Y (2002) The roles of Fzy/Cdc20 and Fzr/Cdh1 in regulating the destruction of cyclin B in space and time. **J. Cell Biol.** *157*, 1139–1149.

For further publications, see numbers 38, 39, 41 and 79 on pages 54, 55 and 57.

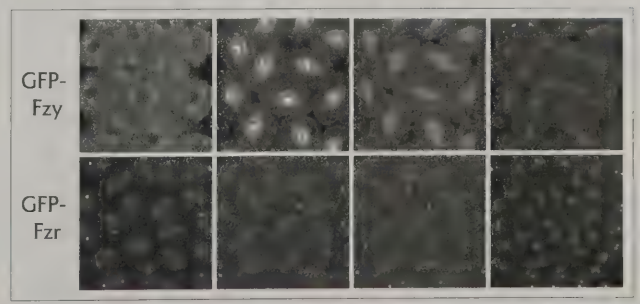
D-TACC stabilises microtubules by recruiting Msps/XMAP215 to centrosomes in *Drosophila* embryos. (A) In normal fly embryos D-TACC recruits the microtubule stabilising protein Msps/XMAP215 to the centrosome. (B) In *dtacc* mutant embryos Msps is no longer recruited to centrosomes, and microtubules are destabilised (seen here by a shortening of the mitotic spindle). (C) In embryos overexpressing D-TACC, extra Msps is recruited to the centrosome/spindle, and microtubules are stabilised (seen here by the elongation of the mitotic spindle). (D) The recruitment of Msps to centrosomes/spindles by D-TACC is specific, and other centrosomal proteins such as γ-tubulin, are not recruited to centrosomes by the overexpression of D-TACC.





The interaction between the TACC proteins and Msps/XMAP215 is conserved. (A) Depleting X-TACC from *Xenopus* egg extracts leads to a shortening of the half spindle microtubules (red) that form around sperm nuclei (blue) when compared to the half spindles that form in mock depleted extracts. (B) Quantitation of half spindle length in X-TACC- and mock-depleted frog egg extracts

Facing page:
GFP-Fzr is rapidly turning over at centrosomes. By bleaching the fluorescence of GFP-Fzr in a small area of an embryo and monitoring the rate of fluorescence recovery (a fluorescence recovery after photo bleaching, or FRAP, experiment) we can show that although GFP-Fzr is strongly concentrated at centrosomes, it is rapidly exchanging with a cytoplasmic pool of GFP-Fzr.



The APC/C regulators Fzy/Cdc20 and Fzr/Cdh1 are concentrated at centrosomes. In living syncytial embryos, GFP-Fzy is concentrated at centrosomes and kinetochores during mitosis while GFP-Fzr is concentrated only at centrosomes.



Co-workers:

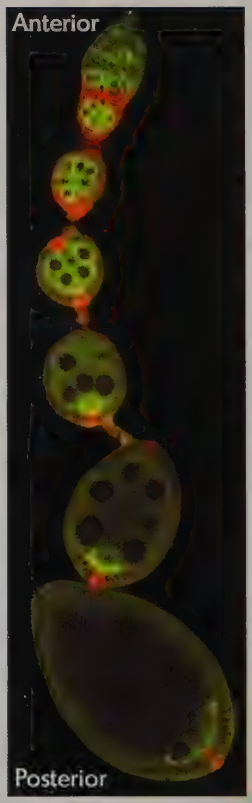
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The localisation of *bicoid* and *oskar* mRNAs to the anterior and posterior poles of the *Drosophila* oocyte defines the AP axis of the embryo, and provides an excellent model for analysing the molecular mechanisms that underlie cell polarity and mRNA localisation. We are taking a combination of cell-biological, genetic and molecular approaches to investigate these mechanisms:

1) The dsRNA-binding protein, Staufen, is required for the microtubule-dependent localisation of *bicoid* and *oskar* mRNAs, and for the actin-dependent localisation of *prospero* mRNA in neuroblasts. We are investigating how Staufen mediates mRNA transport along both actin and microtubules, and are analysing other proteins required for these processes. Since Staufen co-localises with these mRNAs, we are also using GFP-Staufen to visualise mRNA transport *in vivo*;

2) We have shown that the homologues of three genes required for AP axis formation in *C. elegans* (*PAR-1*, *LKB1* [*PAR-4*], and *14-3-3* [*PAR-5*]) are required for the polarisation of the oocyte. Furthermore, mutants in these genes disrupt epithelial polarity. We are now screening for other components of this conserved polarity pathway, and are analysing how it regulates the cytoskeleton;

3) Since many proteins involved in mRNA transport or cell polarity are required throughout development, they were not identified in the classical screens for mutations that disrupt axis formation. To overcome this problem, we are performing screens in germline clones for mutants that affect GFP-Staufen localisation. We have identified many novel genes required for the polarisation of the oocyte or for the localisation of *bicoid* or *oskar* mRNA, and are now analysing their functions.



Martin SG and St Johnston D (2003) A role for LKB1 in *Drosophila* anterior-posterior axis formation and epithelial polarity. **Nature** *421*, 379–384.

Benton R, Palacios IM and St Johnston D (2002) *Drosophila 14-3-3/PAR-5* is an essential mediator of *PAR-1* function in axis formation. **Dev. Cell** *3*, 659–671.

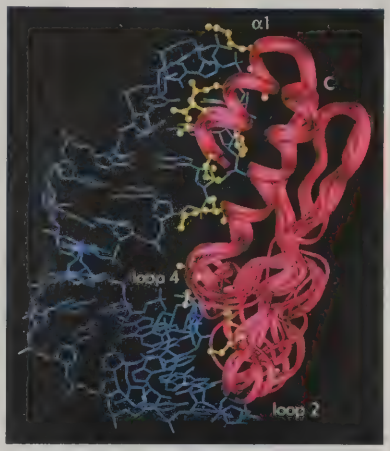
Palacios IM and St Johnston D (2002) *Kinesin light chain*-independent function of the *Kinesin heavy chain* in cytoplasmic streaming, and posterior localization in the *Drosophila* oocyte. **Development** *129*, 5473–5485.

For further publications, see numbers 11, 52, 71 and 95 on pages 53 and 55–57.

Facing page:
A *Drosophila* ovariole, containing a series of germline cysts (green, BicD) that progress through oogenesis as they move posteriorly. The cysts are born at the anterior of the ovariole, and become surrounded by somatic follicle cells (red, FasIII) as they exit the germarium. Each cyst contains 16 germ cells. One of these is selected to become the oocyte and accumulates higher levels of BicD protein.



The localisation of *bicoid* mRNA (black) and *oskar* mRNA (red) to the anterior and posterior poles, respectively, of the stage 10 oocyte.



NMR structure of one double-stranded RNA binding domain from Staufen protein (pink) bound to a 12bp RNA stem-loop (blue). The amino acid side chains that contact the RNA are shown in yellow. Collaboration with Andres Ramos and Gabrielle Varani (LMB-MRC).



Mutants in *LKB1* disrupt *oskar* mRNA localisation and the polarity of the microtubule cytoskeleton. The figure shows the localisation of GFP-Staufen (green; left), *oskar* mRNA (purple; centre) and microtubules (right) in wildtype oocytes (top), and in *lkb1* mutant germline clones (bottom)



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Our research uses the amphibian species *Xenopus laevis* to investigate the formation of the mesoderm during vertebrate development. We are interested in studying mesoderm-inducing signals such as activin, the nodal-related proteins and derrière, in the range over which these factors can act, in their signal transduction pathways (especially the Smad proteins), and in the genes that are activated as immediate-early responses to induction. Transgenic *Xenopus* embryos are used to study how these immediate-early genes are regulated and to identify their targets. We are also analysing the regulation of the cell cycle in the mesoderm, and are making extensive use of morpholino anti-sense oligonucleotides to block gene function, both in *Xenopus laevis* and in the diploid species *Xenopus tropicalis*.

Much of our work concentrates on the *T box* gene family, and especially *Brachyury*, which responds to mesoderm-inducing factors in a strict dose-dependent fashion and which, when mis-expressed, can cause prospective ectodermal cells to form mesoderm. One issue concerns the specificity of *T box* gene action, and to investigate this question we are searching for proteins that interact with *Brachyury* and *VegT*. *Brachyury* is also required for the morphogenetic movements of gastrulation, and we have identified *Wnt11* as a target of *Brachyury* that is required for gastrulation movements in both *Xenopus* and zebrafish. *Wnt11* signals through the planar cell polarity pathway, and we are analysing how components of this pathway control gastrulation, using cell biology and imaging techniques. We also plan to investigate the functions of other *Brachyury* targets such as members of the Bix family of homeodomain-containing proteins.



Xenopus embryos showing expression of *Brachyury* at the early gastrula (top left-hand three embryos) and late gastrula (bottom right-hand three embryos) stages. The embryo in the middle is at an intermediate stage.

Conlon FL, Fairclough L, Price BMJ, Casey ES and Smith JC (2001) Determinants of *T box* protein specificity. **Development** *128*, 3749–3758.

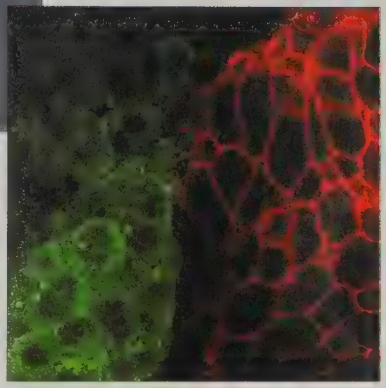
Papin C, van Grunsven LA, Verschueren K, Huylebroeck D and Smith JC (2002) Dynamic regulation of *Brachyury* expression in the amphibian embryo by *XSIP1*. **Mech. Dev.** *111*, 37–46.

White RJ, Sun BI, Sive HL and Smith JC (2002) Direct and indirect regulation of *derrière*, a *Xenopus* mesoderm-inducing factor, by *VegT*. **Development** *129*, 4867–4876.

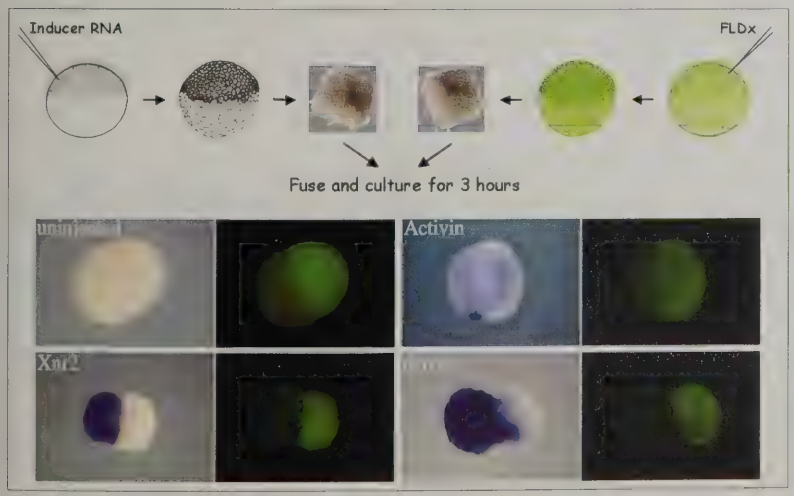
For further publications, see numbers 56, 91, 92, 93, 94 and 103 on pages 55, 57 and 58.

Induction of cell death in the early *Xenopus* embryo is visualised by means of the TUNEL technique, in which apoptotic cells are stained blue.





To investigate the long-range effects of activin, cells expressing a GFP-tagged form of the inducing factors (left) are juxtaposed with cells expressing a red fluorescent membrane marker (right)



Scheme to investigate the signalling ranges of different mesoderm-inducing factors. One embryo (left) is injected with RNA encoding the inducing factor in question, and another (right) with the cell lineage label FLDx. The embryos are allowed to develop to the late blastula stage, when animal pole regions are dissected from the embryos and juxtaposed. Expression of *Xenopus Brachyury* (*Xbra*, blue) is monitored three hours later. *Brachyury* expression does not extend beyond the confines of Xnr2-expressing cells, but a halo of expression is observed in the lineage-labelled cells in response to activin. Derrière can also activate *Xbra* expression in lineage-labelled cells, but its ability to exert long-range effects is more limited than that of activin



Co-workers:

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Atilla Toth
Patrick Western

We are investigating the molecular mechanisms for the specification of primordial germ cells (PGCs) in mice, and of the unique epigenetic reprogramming of the genome that follows subsequently in this lineage. To elucidate the mechanism of germ cell specification, we have developed single cell analysis of nascent germ cells and their somatic neighbours, which share common ancestry. A key feature of PGC specification is the transcriptional repression of region-specific Hox genes and others, but not of genes associated with pluripotency. This is not the case in the neighbouring somatic cells (Figs 1 and 2). Our studies will elucidate how PGCs escape from a somatic cell fate. We are also exploring the relationship between the germ line and pluripotent stem cells, together with the molecular basis for pluripotency and the role of shared gene expression in germ line and stem cells.

As PGCs proliferate and migrate into developing gonads at E10.5 (Fig 3), they undergo extensive epigenetic modifications, including genome-wide DNA demethylation and reactivation of the X chromosome (Fig 4). We are investigating the identity of the intrinsic factors involved in this reprogramming event to elucidate how epigenetic states can be reversed in cell-based assays (Figs 4 and 5), together with their consequences for cell potency. Some of these critical factors are likely to be present in the oocyte. Amongst the known maternally inherited epigenetic modifiers in the oocytes are HP1, Ezh(2) and Eed, which regulate and enhance the epigenetic asymmetry between parental genomes in the totipotent zygote. The precise roles of these and other epigenetic modifiers in regulating early development are being investigated.

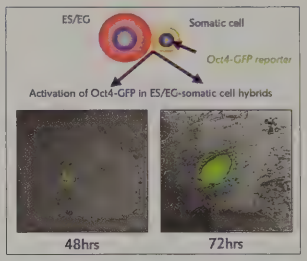


Figure 5. Somatic cells with a reporter transgene, Oct4-GFP, which is expressed following fusion with pluripotent ES/EG stem cells when the somatic nucleus undergoes reprogramming to pluripotency.

Surani MA (2001) Reprogramming of genome function through epigenetic inheritance. **Nature** *414*, 122–128.

Saitou M, Barton SC and Surani MA (2002) A molecular programme for the specification of germ cell fate in mice. **Nature** *418*, 293–300.

For further publications, see numbers 4, 5, 31, 46, 68, 97, 98 and 100 on pages 53–56 and 58.

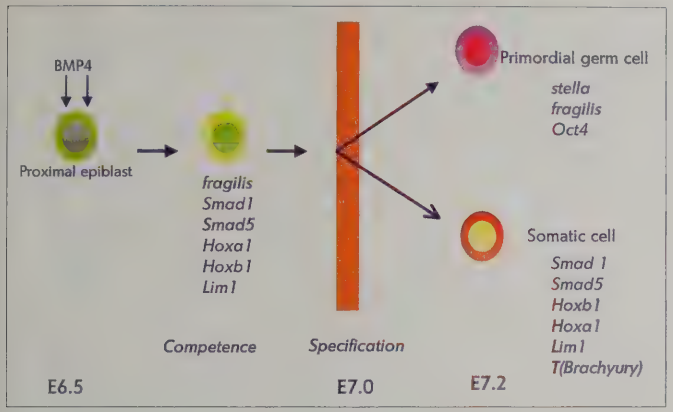


Figure 1. Specification of nascent primordial germ cells. The proximal epiblast cells acquire germ cell competence in response to signalling molecules, including BMP4. Some of these cells acquire PGC fate subsequently, which is associated with transcriptional repression of genes that are expressed in the neighbouring cells, including *Hox* and *Smad* genes. PGCs continue to express pluripotent-specific genes such as *Oct4* and *stella*, a lineage specific gene that is a definitive marker of nascent PGCs.

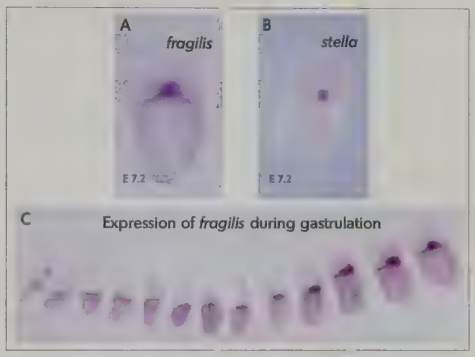


Figure 2. (a) Expression of *fragilis* in a cluster of cells (b) Nascent PGCs, which show expression of *stella* at E7.2. (c) Expression of *fragilis* intensifies during gastrulation as these cells migrate to the posterior proximal region. PGCs are recruited from amongst those cells with the highest expression of *fragilis*, which is followed by expression of *stella*

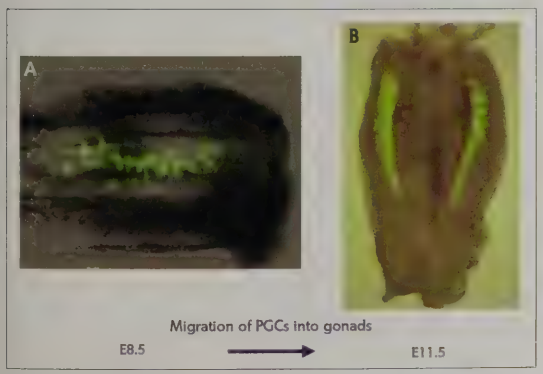


Figure 3. Expression of stella-GFP reporter transgene in (a) migrating, and (b) gonadal PGCs.

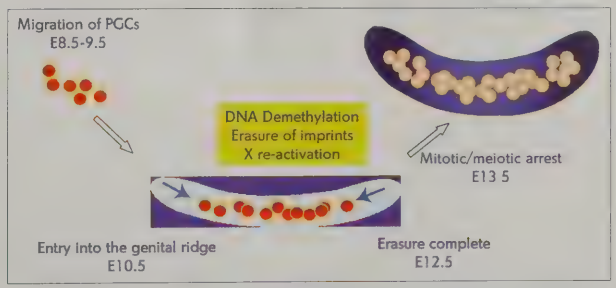


Figure 4. Epigenetic reprogramming of PGCs when they enter the genital ridge at E10.5



Co-workers:

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Dionne Gray
Karin Lykke-Andersen
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Catherine Moore
Jie Na
Karolina Piotrowska
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Bedra Sharif
Maria Elena Torres Padilla

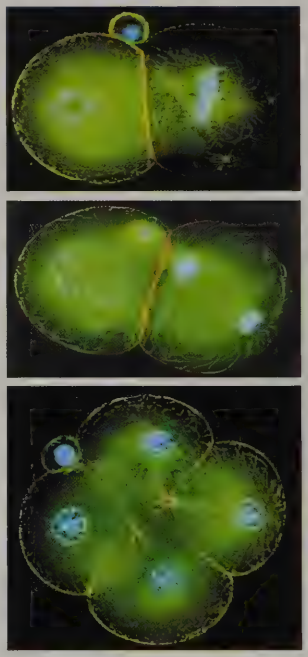
We are studying how polarity and patterning become established during early mouse development. Whereas in most species the polarity of the embryo is laid down in the egg, mammalian embryos were thought to be exceptional, developing their polarity apparently only after implantation. However, our recent cell fate studies showed that mouse embryo organisation and polarity are anticipated before implantation and relate to spatial patterning of the egg. This was unexpected because preimplantation embryos can withstand experimental perturbations and still develop normally. We therefore now aim to understand the mechanisms that establish polarity in normal development and those that compensate for developmental perturbation. Specification of embryonic polarity appears to stem from the position of the meiotic divisions in the egg and the site of sperm entry. The pattern of cell division is influenced by these cues and can dictate the basic features of blastocyst organisation and hence influence the patterning of later stages. These surprising findings open several questions about the origin of polarity in mammals.

We address the following:

1) How do developmental cues lead to initial asymmetry? To address this question we combine experimental and molecular embryology to disturb and examine the role of egg polarity in early patterning;

2) How does polarity of the preimplantation embryo lead to organised signalling activity at later developmental stages? We are using lineage and transplantation studies to examine the normal fate of cells and their fate in novel combinations;

3) What are the mechanisms that establish polarity? We are applying microarray analysis to discover genes that mediate the development of polarity and then perturbing spatial and temporal patterns of expression of such genes through mis-expression and RNA interference.



Mouse embryo undergoing second cleavage division. Orientation of the cleavage plane relates to the animal pole. Microtubules (green), actin (red) and chromatin (blue).

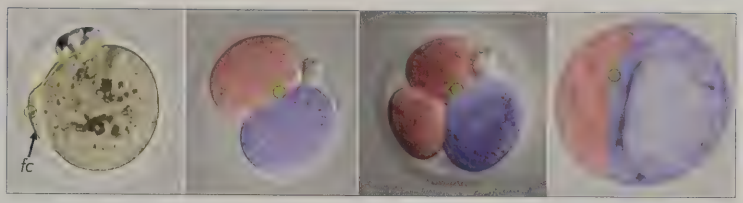
Plusa B, Grabarek JB, Piotrowska K, Glover DM and Zernicka-Goetz M (2002) Site of the previous meiotic division defines cleavage orientation in the mouse embryo. **Nat. Cell Biol.** *10*, 811–815.

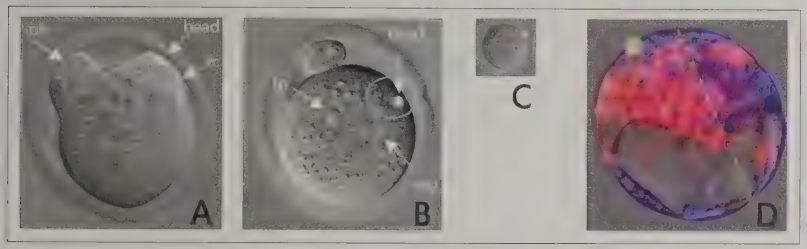
Zernicka-Goetz M (2002) Patterning of the embryo: the first spatial decisions in the life of a mouse. **Development** *129*, 815–829.

Piotrowska K and Zernicka-Goetz M (2001) Role for sperm in spatial patterning of the early mouse embryo. **Nature** *409*, 517–521.

For further publications, see numbers 32, 42 and 75 on pages 54–56.

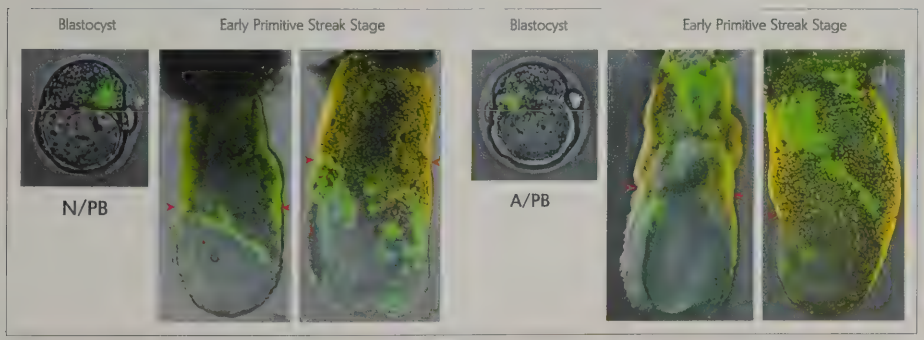
Blastomeres of the 2-cell mouse embryo have distinguishable fates. The fertilisation cone (fc) with sperm tail (yellow) and fluorescent bead (green) marks the sperm entry point (SEP) in the zygote. The 2-cell blastomere that inherits the SEP (red) tends to divide first to produce cells that populate the embryonic part of the blastocyst. The other blastomere (blue) tends to populate the abembryonic part of the blastocyst.





Disruption of the cortical cytoplasm associated with the position of the sperm entry disturbs spatial patterning of the blastocyst. (A) Fertilisation cone (fc) marked by fluorescent bead at the time of polar body (pb) extrusion. (B) After the male pronucleus (mp) had migrated towards the female pronucleus (fp), the cortex and the associated cytoplasm marked by the bead was removed (C). The site of the operation was re-labelled with another bead. 2-cell blastomeres were labelled by dyes and the distribution of their progeny was examined by confocal sectioning at the blastocyst stage. (D) The clonal border of the 2-cell stage progeny (marked by yellow line) is tilted with respect to the blastocyst embryonic–abembryonic boundary.

Polarity of the blastocyst anticipates proximo-distal polarity of the post-implantation embryo. Microinjection of GFP mRNA into inner cell mass cells either near (N/PB) or away (A/PB) from the polar body demonstrates differential fate in the post-implantation egg cylinder.

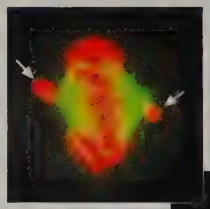


FANNI GERGELY

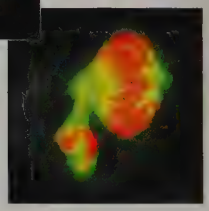


As the primary microtubule organising centre of animal cells, the centrosome ensures the bipolarity of the cell division process, a function that is essential for the accurate partitioning of the genome. Centrosome defects have been implicated in chromosome mis-segregation and the generation of genomic instability, commonly observed in tumours.

My research aims to understand how proteins in the centrosome regulate microtubule behaviour in humans. Homologues of the centrosomal TACC proteins in lower eukaryotes are known to promote microtubule stability during embryonic cell divisions. The role of the human TACC proteins however remains unknown. My recent work has shown that hTACC3 and its interactor ch-Tog are both essential for establishing a functional bipolar spindle in somatic cells. By developing an RNAi-based technique, I intend to investigate additional centrosome residing proteins, in particular the relevance of their localisation to their function.



Chromosomes are mis-aligned (arrows) in hTACC3-depleted human cells.



Mitotic spindles are often multipolar in ch-Tog-depleted cells.

Microtubules are in green, chromosomes are in red.

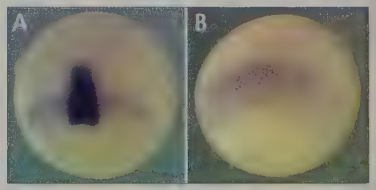
Gergely F (2002) Centrosomal TACCtics. **Bioessays**, *24*, 915–925

For additional publication, see number 39 on page 54.

MIRANDA GOMPERTS



We are studying the regulation and the function of the *Xnot* gene. *Xnot* is expressed in the notochord and pineal gland, and studies in zebrafish reveal that it is necessary to form these tissues. Regulation of the gene is being studied using transgenesis in *Xenopus* and a number of putative transcription factor binding sites have been identified. *Xnot* function is being revealed by a morpholino-based gene knock down approach. We have used morpholinos that inhibit translation and those that interfere with splicing. We have found that, in addition to specifying the notochord, *Xnot* also regulates gastrulation movements.



Gastrula staged embryos stained to reveal *Xnot* RNA transcripts:
A) control MO injected embryo.
B) embryo injected with a morpholino that blocks *Xnot* splicing. Inhibition of splicing prevents *Xnot* transcripts from leaving the nucleus and causes embryos to develop in the absence of a notochord.

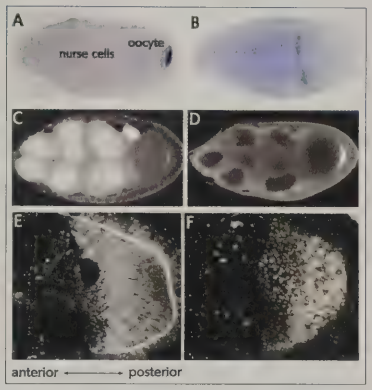
Co-worker:

Kim Goldstone

ISABEL PALACIOS



Intracellular localisation of messenger RNA (mRNA) is a common way of targeting proteins to the regions where they are required. One of the best characterised examples of localised mRNA is found in the *Drosophila* oocyte, where the microtubule-dependent localisation of *oskar* mRNA to the posterior pole of the oocyte specifies the formation of the pole plasm. Genetic screens have identified genes that are specifically required for the transport of *oskar* mRNA, such as *staufen*, *mago nashi*, *barentsz* and *kinesin heavy chain*, but the precise mechanism for localisation has not yet been elucidated. The aim of my research is to understand this mechanism by analysing the function of those factors. I am taking several approaches to address this question: 1) using GFP-Staufen to visualise mRNA transport *in vivo*; 2) searching for new components of the *oskar* mRNA complex; and 3) studying how *kinesin heavy chain*, a microtubule motor protein, recognises the *oskar* mRNA complex and localises it to the posterior pole. Interestingly, in the oocyte the *kinesin heavy chain* can function independently of the *kinesin light chain*, an essential component of Kinesin I, indicating that the *kinesin heavy chain* associates with its cargoes by a novel mechanism.



Localisation of *oskar* mRNA at (A) the posterior or (B) the anterior pole in wild type or *barentsz* mutant oocytes, respectively.

Mago nashi and *Staufen* proteins co-localise with *oskar* mRNA at the posterior pole. However, (C) *Mago* is predominantely nuclear and (D) *Staufen* is cytoplasmic.

The *Kinesin heavy chain* (*Khc*), but not the light chain, is required for the localisation of *oskar* mRNA and Dynein to the posterior (data not shown), and for the cytoplasmic streaming in the oocyte (compare (E) wild type with (F) *Khc* mutant).

Palacios IM and St Johnston D (2002) *Kinesin light chain*-independent function of the *Kinesin heavy chain* in cytoplasmic streaming and posterior localisation in the *Drosophila* oocyte. **Development** *129*, 5473–5485.

For further publications, see 10 and 71 on pages 53 and 56.

CATEGORIES OF APPOINTMENT

Senior Group Leader
Professor, Reader or Lecturer Level
Group Leader
5-year grant-funded appointment (maximum 10 years)
Career Development Fellow
4-year grant-funded appointment, within individual groups
Independent Senior Research Associate
3-year grant-funded appointment, within individual groups
Research Associate/Fellow
Postdoctoral Fellow, within individual groups, appointed by group leader
Research Assistant
Postgraduate, within individual groups, mainly grant-funded
Graduate Student
3-year studentship within individual groups, mainly grant-funded
Research Technician
Within individual groups, mainly grant-funded
Laboratory Assistant
Within individual groups or part of core support, grant-funded

POSTGRADUATE OPPORTUNITIES

As part of the University of Cambridge, the Institute welcomes enquiries from prospective graduate students. We have a thriving population of graduates who contribute greatly, not only to the stimulating research environment, but also to the life of the Institute as a whole. Additionally, graduates become members of the biological or medical sciences department to which their group is affiliated. Graduate studentships are supported mainly by the Wellcome Trust or Cancer Research UK but additional sponsorship may be solicited from a variety of sources, including government research councils. Applicants should write, in the first instance, to the leader of the group they wish to join.

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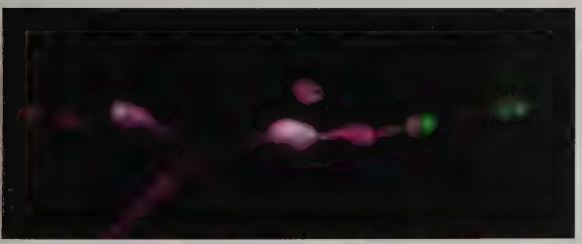
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BBSRC Research Associate



FRET (Fluorescence Resonance Energy Transfer) between GFP and a fluorescent dye revealed at the distal tip of a neuromuscular synapse (Peter van Roessel, 2002).

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KATHY HILTON HNC
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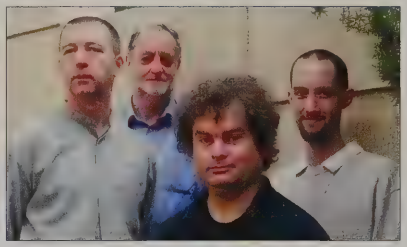
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LINDA ADAMS
GAY CHALKIN
MARGARET HALL
MARGARET THODAY



The following is a list of articles by members of the Institute that were either published or accepted for publication in 2002.

1 Adams IR and McLaren A (2002) Sexually dimorphic development of mouse primordial germ cells: switching from oogenesis to spermatogenesis. **Development** *129*, 1155–1164.

2 d'Adda di Fagagna F, Weller GR, Doherty AJ and Jackson SP (2003) The Gam protein of bacteriophage Mu is an orthologue of eukaryotic Ku. **EMBO Rep.** *4*, 47–52.

3 Ahringer J (2003) Control of cell polarity and mitotic spindle positioning in animal cells. **Curr. Opin. Cell Biol.** *15*, 73–81.

4 Arney KL, Bao S, Bannister AJ, Kouzarides T and Surani A (2002) Histone methylation defines epigenic asymmetry in the mouse zygote. **Int. J. Dev. Biol.** *46*, 317–320.

5 Arney KL, Erhardt S and Surani MA (2002) Genomic imprinting. **Adv. Dev. Biol. Biochem.** *12*, 234–264.

6 Ashrafi K, Chang F, Watts J, Fraser A, Kamath RS, Ahringer J, and Ruvkun G (2003) Genome-wide RNAi analysis of *C. elegans* fat regulatory genes. **Nature** *421*, 268–272.

7 Bannister AJ, Schneider R and Kouzarides T (2002) Histone methylation: dynamic or static? **Cell** *109*, 801–806.

8 Bauer U-M, Daujat S, Neilsen S, Shah, Nightingale K and Kouzarides T (2002) Methylation at arginine 17 of histone H3 is linked to gene activation. **EMBO Rep.** *3*, 39–44.

9 Bell SD, Botting CH, Wardleworth BN, Jackson SP and White MF (2002) Alba, a conserved archaeal chromatin protein, interacts with Sir2 and is regulated by acetylation. **Science**, *296*, 148–151

10 Benton R, Palacios IM and St Johnston D (2002) *Drosophila 14-3-3/PAR-5* is an essential mediator of *PAR-1* function in axis formation **Dev. Cell** *3*, 659–671.

11 Benton R and St Johnston D (2002) Cell polarity: posterior par-1 prevents proteolysis. **Curr. Biol.** *12*, R479–R481.

12 Bernstein BE, Humphrey EL, Erlich RL, Schneider R, Bouman P, Liu JS, Kouzarides T and Schreiber R (2002) Methylation of histone H3 Lys 4 in coding regions of active genes. **Proc. Natl Acad. Sci. USA** *99*, 8695–8700.

13 Blackshaw S and Livesey FJ (2002) Applying genomics technologies to neural development. **Curr. Opin. Neurobiol.** *12*, 110–114.

14 Bökel C and Brown NH (2002) Integrins in development: moving on, responding to, and sticking to the extracellular matrix. **Dev. Cell** *3*, 311–321.

15 Bossing T, Barros CS and Brand AH (2002) A rapid tissue specific expression assay in living embryos. **genesis** *134*, 123–126.

16 Bossing T and Brand AH (2002) Dephrin, a transmembrane ephrin with a unique structure, prevents interneuronal axons from exiting the *Drosophila* embryonic CNS. **Development** *129*, 4205–4218.

17 Bourillot P-Y, Garrett N and Gurdon JB (2002) A changing morphogen gradient is interpreted by continuous transduction flow. **Development** *129*, 2167–2180.

18 Brand AH and van Roessel PJ (2003) Region-specific apoptosis limits neural stem cell proliferation. **Neuron** *37*, 185–187.

19 Brown NH, Gregory SL. Rickoll WL, Fessler LI, Prout M, White RAH and Fristrom JW (2002) Talin is essential for integrin function in *Drosophila*. **Dev. Cell** *3*, 569–579.

20 Burgers WA, Fuks F and Kouzarides T (2002) DNA methyltransferase get connected to chromatin. **Trends Genet.** *18*, 275–277.

21 Byrne JA, Simonsson S and Gurdon JB (2002) From intestine to muscle: nuclear reprogramming through defective cloned embryos. **Proc. Natl Acad. Sci. USA** *99*, 6059–6063.

22 Chalmers A, Welchman D and Papalopulu N (2002) Intrinsic differences between the superficial and deep layers of the *Xenopus* ectoderm control primary neuronal differentiation. **Dev. Cell** *2*, 171–182.

23 Chang J-H, Kim H-C, Hwang K-Y, Lee J-W, Jackson SP, Bell SD and Coy Y (2002) Structural basis for the NAD-dependent deacetylase mechanism of Sir2. **J. Biol. Chem.** *277*, 34489–34498.

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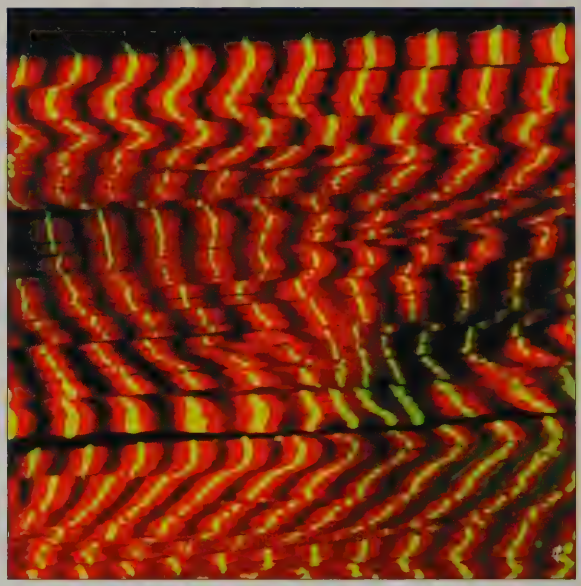
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This figure shows a 3rd instar larval muscle. Phalloidin which stains actin is in red. In green is a transgene of GFP fused to the head domain of the Talin protein (Guy Tanentzapf, 2002).

STAFF AFFILIATIONS

JULIE AHRINGER is a Board Member of the British Society for Developmental Biology, and is a member of the Scientific Advisory Board of Genome Knowledgebase.

ANDREA BRAND is on the Scientific Advisory Board of the Promega Corporation, is a Research Fellow at King's College, and is the Institute representative to the Cambridge University Women in Science, Engineering and Technology Initiative (WiSETI).

NICK BROWN is a member of the Medical Research Council Cross-Board Group.

JOHN GURDON was Master of Magdalene College, Cambridge until 30.09.02; Member, Conseil Scientifique of the Institut Curie, Paris, France; Member, the Scientific Advisory Board of the Max-Planck-Institut für Biophysikalische Chemie, Göttingen; and Chairman of the Company of Biologists.

STEVE JACKSON is a member of the Biochemical Society Nucleic Acids and Molecular Biology Group Committee, Chief Scientific Officer, KuDOS Pharmaceuticals Ltd and Fellow of the Academy of Medical Sciences.

TONY KOUZARIDES is a member of the Cancer Research UK Scientific Executive Board, a member of the Marie Curie Institute Scientific Committee, and non-executive director of AbCam Ltd and Chroma Therapeutics.

ANNE McLAREN is a member of the European Life Sciences Group, the European Group on Ethics (advisory groups to the European Commission) and a Trustee of the Natural History Museum.

NANCY PAPALOPULU is a Board Member of the British Society for Developmental Biology.

JONATHON PINES is a committee member of the British Society for Cell Biology, and Member of the European Molecular Biology Organization.

JORDAN RAFF is a member of the Academy of Medical Sciences' working group on the Careers of Basic Scientists, and was made a life-long member of the Royal Institution.

DANIEL ST JOHNSTON is a Director of the Wellcome Trust Four-Year PhD programme in Developmental Biology at the University of Cambridge, and is a non-executive Director of the Company of Biologists.

JIM SMITH was appointed to the Board of the Babraham Institute and is a member of the Wellcome Trust Basic Science Interest Group. He was made Editor-in-Chief of *Development*

AZIM SURANI is a member of the Royal Society International Exchange Panel, and a member of the Royal Society Working Group on Stem Cells.

MAGDALENA ZERNICKA-GOETZ is a Stanley Elmore Research Fellow at Sidney Sussex College and EMBO Young Investigator.

HONOURS AND AWARDS

JIM SMITH – William Bate Hardy Prize, 2001.

MAGDALENA ZERNICKA-GOETZ – EMBO Young Investigator Award.

ANNE McLAREN – Japan Prize, 2002.

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CHAIRMAN OF THE MANAGEMENT COMMITTEE

PROFESSOR SIR TOM BLUNDELL, Head, Department of Biochemistry, University of Cambridge, UK.

LEAVERS DURING 2002

KATHARINE ARNEY has taken up a postdoctoral position in the laboratory of Dr Amanda Fisher, MRC Clinicial Sciences, Hammersmith Hospital, London.

NIALL ARMES has established ASM Scientific (UK) at Babraham, Cambridge.

UTA-MARIA BAUER now leads her own group at the University of Marburg in Germany.

CHRISTIAN BÖKEL is a postdoctoral fellow at the Max Planck Institute for Cell Biology and Genetics, Dresden, Germany.

PIERRE-YVES BOURILLOT has been awarded a permanent position at the Ecole Normale Supérieure in Lyons, France.

PENNY DAY is pursuing her postdoctoral career.

JESSICA DOWNS has set up her own group in the Department of Biochemistry, University of Cambridge.

VIJI MYTHILY DRAVIAM has taken up a postdoctoral position at MIT (Cambridge, USA) in the laboratory of Peter Sorger.

ANDREW FRASER has taken up a Group Leader position at the Sanger Centre, Cambridge.

ELENA FINEBERG has transferred to the MRC Laboratory for Molecular Biology, Cambridge.

JOHN FREEMAN is continuing his studies.

MONICA GOTTA has taken up a Professorship at ETH, University of Zurich.

MARCUS HICKS is studying in Brazil.

JEAN-RENÉ HUYNH is now working at the Institute Jacques Monod, Paris.

RAVI KAMATH is doing medical school rotations at Harvard University.

SANJEEV KHOSLA has set up his own group at the Centre of DNA Fingerprinting & Diagnostics, Hyderabad, India.

SARA MERCURIO is completing her PhD and takes up a postdoctoral position early in the new year.

TRACY MORAN has returned to forensic science.

OLAF PIEPENBURG now works with Niall Armes at ASM Scientific (UK) in Babraham, Cambridge.

MATT POLLI has taken up a postdoctoral position in the lab of Steve Nutt, Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia.

MORVEN REID is continuing her work in Oxford.

PATRICIA RENDLE is now working from home.

JOHN ROUSE now leads his own group at MRC Protein Phosphorylation Unit, University of Dundee.

MARGARIDA RUAS is now working in Oxford.

MARGARET THODAY is now working at Addenbrooke's Hospital, Cambridge.

MARGARET TYCE BUTCHER has moved to the Department of Materials Science & Metallurgy, University of Cambridge.

RICHARD WHITE has a postdoctoral position in the Schilling Laboratory, University of California.

FLORENCE WIANNY has taken up a postdoctoral position at INSERM in Bron Cedex, France.

ROB WOLTHUIS has returned to the National Cancer Institute in Amsterdam.

PHILIP ZEGERMAN now has a postdoctoral position at the Cancer Research UK Clare Hall Laboratories, South Mimms, UK.

PEDER ZIPPERLEN is a research associate at the University of Zurich.

AARON ZORN is now a Group Leader at the Children's Hospital Medical Center in Cincinnati, USA.



Santa Claus came down the Institute chimney on Friday 6th December, much to the amazement of George Chaikin (1yr) and his brother Sam (4yrs). Many thanks to Santa who came all the way from the North Pole, and to Annegret Finlay for organising the party.

Photo by Bill Wang.

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Front cover image: Aborisation of a neuromuscular synapse in *Drosophila*. Microtubules in blue, synaptic vessels in red, post-synaptic membrane in green, and muscle actin in grey (Peter van Roessel, 2002).

Back cover: Retreat 2002.



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